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Definition and Classification of Negative Outcomes in Solid Organ Transplantation

Application in Liver Transplantation

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Objective
This study defined negative outcomes of solid organ transplantation, proposed a new classification of complications by severity, and applied the classification to evaluate the results of orthotopic liver transplantation (OLT).

Summary and Background Data
The lack of uniform reporting of negative outcomes has made reports of transplantation procedures difficult to interpret and compare. In fact, only mortality is well reported; morbidity rates and severity of complications have been poorly described.

Methods
Based on previous definition and classification of complications for general surgery, a new classification for transplantation in four grades is proposed. Results including risk factors of the first 215 OLTs performed at the University of Toronto have been evaluated using the classification.

Results
All but two patients (99%) had at least one complication of any kind, 92% of patients surviving more than 3 months had grade 1 (minor) complications, 74% had grade 2 (life-threatening) complications, and 30% had grade 3 (residual disability or cancer) complications. Twenty-nine per cent of patients had grade 4 complications (retransplantation or death). The most common grade 1 complications were steroid responsive rejection (69% of patients) and infection that did not require antibiotics or invasive procedures (23%). Grade 2 complications primarily were infection requiring antibiotics or invasive procedures (64%), postoperative bleeding requiring >3 units of packed red cells (35%), primary dysfunction (26%), and biliary disease treated with antibiotics or requiring invasive procedures (18%). The most frequent grade 3 complication was renal failure, which is defined as a permanent rise in serum creatinine levels ≥ twice the pretransplantation values (11%). Grade 4 complications (retransplantation or death) mainly were infection (14%) and primary dysfunction (11%). Comparison between the first and last 50 OLTs of the series indicates a significant decrease in the mean number of grade 1 and 2 complications. This was partially a result of better medical status of patients at the time of transplantation. Using univariate and multivariate analyses of risk factors, the best predictor of grade 1 complications was donor

obesity; for grade 2 complications, the best predictor was a donor liver rewarming time of >90 minutes, and for grade 3 and 4 complications, the best predictor was the APACHE II scoring system and donor cardiac arrest.

Conclusions

Standardized definitions and classification of complications of transplantation will allow us to better evaluate and compare results of transplantation among centers and over time, and better compare effectiveness of new therapies. Orthotopic liver transplantation still is a procedure with high morbidity that requires careful analysis of risk factors to optimize selection of patients and organ sharing.

Organ transplantation has enjoyed increasing success in the last decade. Liver, heart, and lung transplantations have emerged from an experimental stage to become the mainstay of treatment of a variety of diseases. In 1990, about 10,000 kidneys, 2700 livers, 200 hearts, 500 pancreases, and 260 lungs were transplanted in the United States.[1] However, despite major advances in organ preservation, anesthesia, surgery, and immunosuppression, there is still considerable mortality and morbidity. In fact, only mortality is well described in the literature—e.g., 15% to 30% from orthotopic liver transplantations (OLT)[2–4]—, whereas morbidity rates have been poorly reported.

The lack of uniform reporting of negative outcomes is a major shortcoming in the medical literature, making interpretation of results of therapies difficult. We recently presented definitions of negative outcomes of general surgery—i.e., sequel, failure to cure, and complications—and proposed a classification of complications by severity.[5] This classification was then applied to open[6] and laparoscopic[7] cholecystectomy, as well as other nonsurgical therapies of cholelithiasis.[8] The classification has allowed us to 1) present an uniform way to report results, 2) compare results of two distinct time periods in a single center, 3) compare results of surgery between different centers, 4) compare results of surgical *versus* nonsurgical therapies, 5) identify objective preoperative risk factors, and 6) establish preoperative prognostic scores. Standardization in reporting negative outcomes will also be a valuable tool in prospective studies of new therapies. Finally, we found that the classification is useful to present potential complications to patients to get their informed consent.

The original classification mainly applies to procedures with relatively low morbidity. For instance, more emphasis was given to "minor events," including asymptomatic problems. Transplantation is associated with more serious complications, and some are specific for transplantation, such as those related to immunosuppression or rejection. Thus, adaptation of the original classification was felt to be necessary for use in organ transplantation.

The primary aim of this study was to define negative outcomes of solid organ transplantation and to propose a new classification of complications by severity. Then, defining specific complications of OLT, results, risk factors, and prognostic scores for OLT were evaluated in the first 215 OLTs performed at the University of Toronto.

METHODS

Definition of Negative Outcome of Solid Organ Transplantation

Negative outcomes are subdivided into three groups as previously presented[5]—i.e., 1) failure to cure, 2) negative sequel, and 3) complication. Failure to cure refers to pre-existing conditions that remain unchanged after the transplantation procedure. This includes recurrence of the primary disease—e.g., recurrence of hepatoma, hepatitis B or C—as well as persistence of pre-existing conditions not related directly to the primary disease—e.g., diabetes or arterial hypertension. Diseases that clearly worsen as a result of transplantation are complications and not a failure—e.g. noninsulin-dependent diabetes that becomes insulin-dependent diabetes. A negative sequel is an adverse outcome inherent to the transplantation procedure—i.e., it is an accepted alteration in structure or function of the body that is embodied in the intervention.[5] Scar, postoperative pain, and need for intensive care unit (ICU) stay are negative sequelae, not complications. Complication is any other negative outcome that does not fit clearly into the definition of negative sequel or failure to cure.

General Classification of Complications by Severity

The general classification is intended as a guide for establishing specific classifications for individual organ transplantation, and thus, emphasizes principles rather

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than details. Subsequently, we will derive a specific classification for OLT to evaluate the results of this procedure in our program.

As in the original classification,[5] the following criteria were used to stratify complication: 1) whether the complication is life threatening, i.e., if left unchecked, would the event normally resolve or go to permanent disability, retransplantation, or death; 2) whether interventions required to treat the complication carry significant risks, with particular negative weight given to invasive procedures; and 3) whether residual disability, retransplantation, or death are induced by the complication. Great reliance has been placed on the therapeutic procedure required to treat the complication to indicate the severity of the complication. This is particularly helpful in retrospective analysis in which complication may not be described in detail, but documentation of diagnostic tests and treatment usually is complete. Another reason for considering diagnostic procedures and treatments in a classification is that they may induce further morbidity. Finally, the emphasis on therapeutic procedures tends to eliminate subjective interpretation of severity and any tendency to down-rate a complication since it is based on objective criteria. Complications are graded in four groups as in the original classification.[5] Additionally, grade 3 and 4 complications have been subdivided into two subgroups.

Grade 1 complications include all events carrying minor risks, even if they result in some prolongation of ICU or total hospital stay. The term minor means that the complication, if left untreated, has a spontaneous resolution, can be cleared by the patient after instruction, or, at most, needs a simple bedside procedure with minor or no analgesia. Drugs are not required other than immunosuppressors, analgesic, antipyretic, anti-inflammatory, and anti-emetic, drugs required for urinary retention or lower urinary tract infection, and drugs required for arterial hypertension, hyperlipidemia, or transient hyperglycemia. Postoperative bleeding requiring up to 3 units of packed red cells also is included.

Grade 2 complications differ from grade 1 complications because they are potentially life threatening and usually require some form of intervention, which is associated with well-described complications. Grade 2 events do not produce lasting or residual disability, and are not malignant (except squamous and basocellular cutaneous cancer).

A large spectrum of complications related to the suffering that the complications may cause to patients is included in this category, as is the risk inherent in some invasive procedures needed to treat the complications. Therefore, as previously described,[5] a subdivision into two strata of severity is made according to the invasiveness of the intervention needed to manage the complication. Grade 2a includes all complications requiring drug therapy other than that allowed for grade 1 complications, total parenteral nutrition, or transfusion of more than 3 units of packed red cells for postoperative bleeding. Any complication resulting in a doubling of the hospital stay—e.g., ≥ 4 weeks for OLT—becomes at least a grade 2a complication. Grade 2b complications are those that require further invasive procedures, including therapeutic imaging procedures (e.g., percutaneous drainage of abscess), therapeutic endoscopy, or reoperation. Any complication that requires readmission to the ICU or significantly extends the ICU stay more than twice the stay for the transplant procedure—e.g. ≥ 5 days for OLT—is a Grade 2b complication.

Grade 3 complications are events with residual or lasting functional disability. The development of malignant disease also is included, with the exception of squamous and basocellular cutaneous malignancies that are considered 2b complications. A myocardial infarct is in this category; any cerebrovascular event with residual disability also is included. A subdivision is made in this group to differentiate nonprogressive complications (grade 3a) from progressive complications (grade 3b). The term progressive refers to a complication that is likely to progress to death or to the development of end-stage graft disease requiring retransplantation.

In the original classification, grade 4 complication is simply a death related to a complication. We have subdivided this group into grade 4a (retransplantation) and grade 4b (death). Retransplantation is included because it indicates complete failure of the first transplant procedure with all the risks inherent to repeated surgery. Additionally, in liver, heart, and lung transplantations, survival of the patient depends on the availability of a suitable organ.

Classification of Complication Following OLT

The most frequent complications of OLT are classified by severity in Table 1. There is no consensus about the definition of primary dysfunction (PDF).[10] Separation between primary nonfunction and initial poor function of the graft has been proposed recently.[11] Our definition includes both entities and emphasizes the treatment necessary—i.e., prolongation of the ICU stay.[10,12] Primary dysfunction was not considered to be a grade 1 complication because minor liver dysfunction is inherent to the procedure, and thus, it is a sequel rather than a complication. Therefore, PDF is at least a grade 2 complication and is considered grade 2a or 2b complication according to the length of stay in the ICU. The need for retransplantation makes PDF a grade 4a complication and death of the patient a grade 4b complication. Thus, grade 4 PDF corresponds to the definition of true primary nonfunc-

Table 1. CLASSIFICATION OF COMMON COMPLICATIONS OF LIVER TRANSPLANTATION

Grade 1	*An alteration from ideal postoperative course with complete recovery or which can be easily controlled and which fulfills the general characteristics namely: a) not life-threatening, b) not requiring use of drugs other than immunosuppressors, analgesics, antipyretic, antiinflammatory and antiemetic, drugs required for urinary retention or lower urinary tract infection, arterial hypertension, hyperlipidemia or transient hyperglycemia, c) requiring only therapeutic procedures that can be performed at the bedside, d) postoperative bleeding requiring ≤3 units of blood, and e) never associated with a prolongation of the ICU stay ≥5 days or total hospital stay ≥4 weeks*
	Examples
	Superficial wound infection treated without antibiotics
	Bile leak treated conservatively
	Acute rejection treated only by an increased in the usual immunosuppression or steroid responsive rejection
	Increase in creatinine levels ≥ twice the pretransplantation values or increase in creatinine levels ≥100 μmol/L (11.2 mg/L) resolving within a week
	Hyperglycemia >11.2 μmol/l (2 g/L) for at least 24 hr and resolving within a week
	Well controlled arterial hypertension
	Hyperlipidemia: cholesterol >6.2 mmol/L (240 mg/dL) or LDL >4.12 mmol/L (160 mg/dL) normalized within 3 months of treatment
Grade 2	*Any complication that is potentially life-threatening or results in ICU stay ≥5 days or hospital stay ≥4 weeks, but which does not result in residual disability or persistent diseases*
Grade 2a	*Complications requiring only use of drug therapy or postoperative bleeding requiring >3 units of blood*
	Examples
	Rejection requiring immunosuppressors not routinely used after induction therapy—e.g., OKT3 or other antilymphocyte drugs
	Transient increase in creatinine levels as defined above for more than a week
	Bacterial, viral or fungal infection requiring antibiotic, antiviral or antifungic therapy
	Primary graft dysfunction (PDF) (opening AST ≥2000 or a transient increase in AST levels ≥1000 IU/L, or a persistent elevated PT >20 over 3 days)
	Transient obesity (BMI ≥30 kg/m^2) or increase in 5 kg/m^2 in preoperative obese patients, transient cachexia with BMI <18 kg/m^2 or decrease of 2 kg/m^2 in preoperative cachectic patients
	Hyperlipidemia as defined above and requiring >3 months of treatment for normalization
	Transient diabetes mellitus requiring hypoglycemic drugs or insulin for ≥7 days
Grade 2b	*Complications requiring therapeutic invasive interventions, readmission in the ICU or prolongation in the ICU stay ≥5 days, but which do not result in residual disability*
	Examples
	Primary graft dysfunction extending the ICU stay ≥5 days
	Postoperative bleeding requiring laparotomy
	Gastrointestinal bleeding treated endoscopically or surgically
	Bile leak requiring endoscopic or surgical procedures
	Bile duct stricture corrected percutaneously, endoscopically or by surgery
	Renal failure requiring transient hemo or peritonealdialysis
	Squamous or basocellular cutaneous tumors
Grade 3	*Any complication with residual or lasting functional disability or development of malignant disease (except squamous and basocellular cutaneous malignancies)*
Grade 3a	*Complication with lasting disability that shows no evidence of progression, and that has a relatively low risk of graft failure and/or death*
	Examples
	De novo hepatitis C
	Nonprogressive chronic rejection
	Persistent bile duct stricture not amenable to surgical or endoscopic treatment without evidence of progressive liver failure or recurrent cholangitis
	Persistent (at least 6 months) elevation of creatinine levels as defined above
	Cardiac arrest or MI without development of significant disability—i.e., status I–II in the New York classification[9]
	Persistent (at least 6 months) morbid obesity or cachexia as defined above
	Persistent (at least 6 months) diabetes mellitus (e.g., with HbACl >0.07)
	Uncorrectable hyperlipidemia as defined above after at least 6 months of treatment
Grade 3b	*Complications with lasting disability that are either difficult to control or have a significant risk of leading to graft failure and/or death*
	Examples
	De novo hepatitis B
	Development of malignancy
	Persistent bile duct stricture not amenable to surgical or endoscopic treatment with progressive liver failure or recurrent cholangitis
	Progressive chronic rejection
	Renal failure requiring persistent (at least 6 months) hemodialysis or renal transplantation
	Cardiac arrest or myocardial infarction with persistence (at least 6 months) of significant disability—i.e., status III–IV in the New York classfication
Grade 4	*Complications that lead to retransplantation (**Grade 4a**) or death (**Grade 4b**)*

tion.[10] There is no grade 3 PDF because we have not identified long-lasting disability related to PDF.

Acute rejection is graded according the response to steroid bolus (grade 1) or the need of antilymphocyte drugs, such as OKT_3 (grade 2). Differentiation is made because the use of antilymphocyte product usually is reserved for steroid-resistant rejection and can induce further morbidity, such as cytomegalovirus infection or malignancies. Histologic evidence of chronic rejection—e.g., vanishing bile duct syndrome—is a grade 3a or 3b complication, respectively, according to the absence or presence of progressive liver failure. Retransplantation for chronic rejection is a 4a complication.

Bile leak is a grade 1 complication if it resolves when treated conservatively. A bile leak or biliary stricture is a grade 2b complication if it requires percutaneous, endoscopic, or surgical procedures for correction. In the presence of uncorrectable multiple strictures, it becomes a grade 3a complication; it becomes a 3b complication in the case of progressive liver failure. Retransplantation because of a biliary problem is a grade 4a complication.

Renal failure is defined according to serum creatinine levels because creatinine clearance measurements rarely are available in the routine follow-up of patients. An increase in creatinine of twice the preoperative level or an increase in creatinine levels $\geq$ 100 μmol/L (11.2 mg/L) was chosen because it indicates at least a 50% decrease of the glomerular filtration rate. Renal failure is a grade 1 complication if it resolves in less than a week, a grade 2a complication if it resolves in more than a week, and a grade 2b complication if transient hemodialysis or peritoneal dialysis is necessary. It is a grade 3a complication if elevated creatinine levels persist for at least 6 months, and a grade 3b complication if long-term dialysis or kidney transplantation are required.

Hyperglycemia, which often is related to steroid therapy, is a grade 1 complication if it resolves within a week and a grade 2a complication if it requires longer treatment. Persistent de novo insulin-dependent or noninsulin-dependent diabetes mellitus for at least 6 months is a grade 3a complication. Hyperlipidemia is a complication because it is associated with major cardiovascular diseases and requires therapy. Cutoff for cholesterol and low-density lipoprotein levels have been chosen according to a consensus conference.[13,14] Hyperlipidemia is a grade 1 complication when it corrects within 3 months, a grade 2a complication when it corrects after more than 3 months, and a grade 3a complication if it is uncorrectable for at least 6 months. Obesity, which is not uncommon in OLT,[15] is a major independent risk factor for cardiovascular diseases and significantly impairs quality of life.[16] For this study, only morbid obesity—according to the criteria defined at a NIH consensus conference[16,17]—is considered a complication. Transient obesity is a grade 2a complication, whereas persistent obesity for at least 6 months is a grade 3a complication. Cachexia is associated with increased morbidity, including susceptibility for infection, and also impairs quality of life. Cutoff also is based according to the NIH consensus conference.[16]

De novo hepatitis C and B can be serious problems. Hepatitis C usually is well tolerated after transplantation,[18] and is considered a grade 3a complication. Conversely, hepatitis B is associated with a high risk of graft failure in immunocompromised patients[19–21] and therefore, is a grade 3b complication, unless it leads to retransplantation or death, which would make it a 4a or 4b complication, respectively. Note that recurrent hepatitis B or C is considered a failure to cure and therefore, is not a complication. All malignancies other than squamous and basocellular cutaneous malignancies are considered at least a 3b complication.

RESULTS

Results of the First 215 Adult OLTs Performed at the University of Toronto

Population

Results of OLT in the first 215 adult recipients transplanted at the University of Toronto between October 1985 and December 1991 have been evaluated using the aforementioned definition and the classification. All survivors had a 1-year follow-up; this is an analysis representative of negative outcomes that occurred during the first year of transplantation. Data was collected from the prospective Multiple Organ and Retrieval and Exchange program of Ontario, the recipients, and ICU databases. All the information was coded, entered into a computer, and analyzed using the Statistical Analysis System.[22] Characteristics of the transplant population are given in Table 2. Sequential immunosuppression was used in all patients using antilymphocyte drugs, such as Minnesota ALG for induction of immunosupression. Cyclosporine was started on postoperative days 4 through 7. Azathioprine was used in patients with cyclosporine nephrotoxicity or for episodes of rejection that occurred despite adequate cyclosporine levels. Specific complications were recorded only once at the highest levels they achieved.

Overall Incidence of Complications and Failure to Cure

Two hundred thirty-five OLTs were performed in 215 patients. Nineteen patients (8.8%) had a second transplantation, and one patient (0.5%) had a third. The incidence of complications and failure to cure is given in Table 3. All but two patients (99.1%) had at least one complication of any kind. More than three quarters of the

Table 2. CHARACTERISTICS OF 215 LIVER TRANSPLANTATION RECIPIENTS

Duration of the study	October 1985–December 1991
Male/female	116/99 (54%/46%)
Median age (range)	48 years (17–72)
Diagnosis	
Hepatitis non A—non B, and C, and idiopathic cirrhosis	45 (20.9%)
Primary biliary cirrhosis	31 (14.4%)
Primary sclerosing cholangitis	24 (11.2%)
Fulminant hepatic failure	24 (11.2%)
Hepatoma-cholangiocarcinoma	22 (10.2%)
Hepatitis B	21 (9.8%)
Alcoholic cirrhosis	19 (8.8%)
α 1 antitrypsin deficiency	10 (4.7%)
Autoimmune hepatitis	6 (2.8%)
Hemochromatosis	4 (1.9%)
Budd-Chiari syndrome	4 (1.9%)
Others	5 (2.3%)
Medical status at the time of listing	
Status 1	114 (53.0%)
Status 2	63 (29.3%)
Status 3	23 (10.7%)
Status 4	15 (7.0%)

Medical status are status 1: patient at home, status 2: patient in hospital or with liver cancer, status 3: patient in an acute care unit not intubated, status 3: patient in the ICU and intubated.

patients had grade 1 or 2 complications. About one fifth of patients had grade 3 complications, mainly grade 3a, and about 30% had grade 4 complications—i.e., a 8% incidence of retransplantation (4a) and a 21% mortality rate from complications (4b).

Assessment of grade 1, 2, and 3 complications is more meaningful when patients who died or were retransplanted within 3 months of OLT were excluded. This is because these seriously ill patients were at very low risk of developing minor (grade 1) or permanent (grade 3) complications. This avoids underestimating the incidence of grade 1, grade 2, or grade 3 complications. In this study, the incidence of grade 1 complications in the first transplantation group rose to 92% (146/159), grade 2 complications rose to 93.1% (n = 148) including 89.9% (n = 143) grade 2a and 45.9% (n = 73) grade 2b complications. Grade 3 complications increased to 30.2% (n = 48).

The actual 1-year mortality rate was 27.0% (58 of 215 patients)—i.e., 21.4% (46 patients) from complications of the first transplant, 2.8% (6 patients) from complications of the second transplant, and 2.8% (6 patients) from failure to cure.

To be able to describe the risk of surgery to a prospective OLT patient, the number of complications per patient may be more informative. In this series, patients had a average of 6.1 complications ranging from 0 to 16 with a median of 5. The average number of grade 1 complications per patients was 2.2 (median = 2, range = 0–9); the average number of grade 2 complications was 3.5 (median = 2, range = 0–10), including an average of 2.8 grade 2a complications (median= 2, range = 0–8) and an average of 0.6 grade 2b complications (median = 0, range = 0–6). The average number of grade 3 complications was 0.3 (median = 0, range = 0–3), including an average of 0.2 grade 3a complications (median = 0, range = 0–2) and an average of 0.05 grade 3b complications (median = 0, range = 0–1).

Failure to cure occurred in 13.5% of the patients, including two retransplantations (0.9%) caused by recurrent Budd Chiari syndrome and recurrent hepatitis B. All six deaths (2.8%) were related to recurrent hepatitis B. Recurrence in the other 21 patients was caused by hepatitis B (n = 11), hepatitis C (n = 8), cholangiocarcinoma (n = 1), and carcinoid tumor (n = 1). Eighty-six per cent (18/21) of patients transplanted for chronic hepatitis B had recurrence of their disease, including six deaths (29%) related directly to the recurrence.

Incidence of Specific Complications

Complications analyzed by diagnosis are presented in Table 4. Any complication, even if concomitant with another one, is listed. Thus, if a patient died from PDF with coexisting intra-abdominal abscess, both PDF and infection are considered grade 4b complications. The most common grade 1 complications was steroid responsive

Table 3. NUMBER AND PERCENT OF PATIENTS WITH COMPLICATIONS AND FAILURE TO CURE IN 215 LIVER TRANSPLANT RECIPIENTS

	1st Transplant (n = 215)	2nd Transplant (n = 19)
Any complication	213 (99.1%)	19 (100%)
Grade 1 complication	163 (75.8%)	14 (74%)
Grade 2 complication	187 (87.0%)	16 (84%)
Grade 2a	175 (81.4%)	12 (63%)
Grade 2b	99 (46.0%)	8 (42%)
Grade 3 complication	49 (22.8%)	3 (16%)
Grade 3a	44 (20.5%)	0
Grade 3b	7 (3.3%)	3 (16%)*
Grade 4 complication	63 (29.3%)	7 (37%)
Grade 4a	17 (7.9%)	1 (5%)
Grade 4b	46 (21.4%)	6 (32%)
Any failure to cure	29 (13.5%)	0
Failure to cure (patient alive)	21 (9.8%)	0
Failure to cure (patient retransplanted)	2 (0.9%)	0
Failure to cure (death)	6 (2.8%)	0

* p = 0.03, Fisher's exact test.

Table 4. NUMBER AND PERCENT OF PATIENTS WITH SPECIFIC COMPLICATIONS AFTER THEIR FIRST LIVER TRANSPLANTATION

	PDF	Rejection	Infection of Any Kind	Postoperative Bleeding	Renal Disease	Biliary Disease	Diabetes	Obesity	Hyperlipidemia
Grade 1	0	110 (69.2%)	36 (22.6%)	19 (11.9%)	18 (11.3%)	10 (6.3%)	12 (7.5%)	0	8 (5.0%)
Grade 2	42 (26.4%)	19 (11.9%)	102 (64.2%)*	56 (35.2%)	33 (20.8%)	28 (17.6%)	12 (7.5%)	9 (5.7%)	10 (6.3%)
Grade 2a	31 (19.5%)	19 (11.9%)	87 (54.7%)	32 (20.1%)	32 (20.1%)	6 (3.8%)	12 (7.5%)	9 (5.7%)	10 (6.3%)
Grade 2b	11 (6.9%)	0	31 (19.5%)	24 (15.1%)	1 (0.6%)	22 (13.8%)	0	0	0
Grade 3	0	4 (2.5%)	0	0	18 (11.3%)	2 (1.3%)	5 (3.1%)	3 (1.9%)	1 (0.6%)
Grade 3a	0	4 (2.5%)	0	0	16 (10.1%)	1 (0.6%)	5 (3.1%)	3 (1.9%)	1 (0.6%)
Grade 3b	0	0	0	0	2 (1.3%)	1 (0.6%)	0	0	0
Grade 4	23 (11.0%)	4 (1.9%)	29 (13.8%)	1 (0.5%)	0	1 (0.5%)	0	0	0
Grade 4a	6 (2.9%)	4 (1.9%)	0	0	0	1 (0.5%)	0	0	0
Grade 4b	17 (8.1%)	0	29 (13.8%)	1 (0.5%)	0	0	0	0	0

* Some patients developed more than one type of infection–i.e., Grade 1a and 2a complications.

Grade 1, 2, and 3 complications are reported excluding all patients who died or where retransplanted within 3 months of transplantation. Total number of patients analyzed for grade 1, 2, and 3 complications is 159 patients. Grade 4 complication is analysed by excluding patients who died or were transplanted due to recurrence of their disease (failure to cure) within 3 months of transplantation. Total number of patients analysed for grade 4 complications is 210 patients.

rejection (69.2% of patients), followed by infection (22.6%). The most frequent grade 2 complications were infection (64.2%), postoperative bleeding (35.2%) and PDF (26.4%). About one third of grade 2 infections required invasive therapy (grade 2b), compared to approximately half of postoperative bleeding. Most grade 2 PDF occurred without significant prolongation of the ICU stay (grade 2a). The most common grade 3 complication was renal failure (11.3%). Other important causes of grade 3 complications were diabetes mellitus (3.1%), rejection (2.5%), and obesity (1.9%). Grade 3b complication was noted in seven patients (3.3%) and was related to malignancies (n = 4), renal failure requiring hemodialysis (n = 2), and multiple biliary strictures with progressive liver failure (n = 1). Grade 4 complications were related predominantly to PDF or infection. The indication for retransplantation (grade 4a) was PDF (n = 6, 2.9%), hepatic artery thrombosis (n = 5, 2.3%), rejection (n = 4, 1.9%), multiple biliary strictures (n = 1, 0.5%), and portal vein thrombosis (n = 1, 0.5%). The 46 fatal cases (grade 4b) were related to sepsis (n = 29, 13.8% of the total patients), PDF (n = 17, 8.1%), cardiovascular diseases (n = 3, 1.4%), malignancies (n = 3, 1.4%), neurologic disorders (n = 2, 0.9%), and postoperative bleeding (n = 1, 0.5%). Renal failure has not been listed in grade 4 complications because it has never been identified as the primary cause of death. However, serum creatinine $\geq$ 200 μmol/L (23 mg/L) was noted in 34.9% (22/63) of patients with grade 4 complications, including 41.2% (7/17) with grade 4a complications and 32.6% (15/46) with grade 4b complications.

Incidence of Complications Over Time

To determine whether the incidence and types of complications changed over time, the results of the initial 50 patients transplanted before June 1988 were compared with the last 50 patients transplanted after May 1991 (Table 5). Grade 1, 2, and 3 complications were evaluated, excluding all patients who died or were retransplanted within 3 months of transplantation; grade 4 complications also were evaluated, excluding patients who died from recurrence of the liver disease within 3 months of their transplant. There was a decrease in all types of complications, reaching statistical significance for overall, grade 1, 2, and 2a complications. The most significant decreases in complications were grade 1 and 2 infection and grade 1 renal failure ($p < 0.02$; Fisher's exact test). To further evaluate the change in the number of complications over time, we calculated the correlation between the transplantation date and the number of complications in the complete series. Using the Spearman (nonparametric) correlation test, the following correlations were identified: all complications, $R = 0.22$ ($p < 0.01$); grade 1, $R = -0.22$ ($p < 0.01$); and grade 2, $R = -0.13$ ($p = 0.08$). Correlation for both grade 3 and 4 was $R = -0.02$ (NS). Both analyses indicate a decrease in the number of complications over time, statistically significant for grade 1 and 2 complications.

To identify whether the decrease in complications relates to improvement in management or better selection of patients, the two groups were compared. The most relevant finding in comparing the initial patients *versus* the last 50 patients of the series was the medical status of listing (status 1:21 *vs.* 32 patients, status 2:10 *vs.* 11 patients, status 3:11 *vs.* 6 patients, and status 4:8 *vs.* 1 patients, respectively). The number of status 3 and 4 patients were significantly higher than the number of status 1 and 2 patients in the early group of patients *versus* the last 50 patients of the series ($p = 0.01$, Fisher's exact test).

Table 5. CHANGE IN THE MEAN NUMBER OF COMPLICATIONS PER PATIENT OVER TIME IN PATIENTS WITH THEIR FIRST TRANSPLANT

	First 50 Recipients	Last 50 Recipients	p Values*
Grade 1	2.79	2.03	0.03
Grade 2	3.70	2.74	0.02
Grade 2a	3.03	2.21	0.03
Grade 2b	0.66	0.53	0.19
Grade 3	0.3	0.2	0.69
Grade 4	0.29	0.27	0.84
Total	6.75	5.08	0.01

* Wilcoxon sign rank test was used to evaluate the number of grade 1-3 complications and Fisher's exact test was used for the presence or absence of grade 4 complications.

However, preoperative APACHE II (10.1 ± 4.5 *vs.* 11.6 ± 4.9), Pugh (10.3 ± 2.9 *vs.* 9.8 ± 2.9), and Shaw (3.7 ± 2.8 *vs.* 3.9 ± 2.6) scores were not statistically different between the groups. Other factors, such as the use of Eurocollins/University of Wisconsin (UW) solution (44/6 *vs.* 0/50, $p < 0.001$, Fisher's exact test), decrease in the warm ischemia time (71.5 *vs.* 55 minutes, p=0.003, Wilcoxon sign rank test) also may have been important in the decrease incidence of complications over time. Similar conclusions are drawn if patients who died or were retransplanted within 3 months of their transplant were excluded from the analysis. Thus, decrease of complications later in the series was related to better medical status of patients at the time of listing. Improved management also may have played a role.

Prognostic Scoring Systems and other Risk Factors of Complications

Preoperative Scoring Systems

Three preoperative score systems were evaluated—APACHE II, Pugh, and Shaw scores. The APACHE II score is based on objective physiologic measurements, age, and previous health status. It has been designed to predict the outcome of patients in a mixed medical and surgical population in the ICU[23] and also has been shown to predict mortality in other conditions.[24-27] The maximum theoretical score is 71, but no score above 55 has been reported. The following three score categories were defined: low, ≤ 8, intermediate, 9–12, and high, ≥ 13. The Pugh score[28] is a modification of the Child-Turcotte classification that assesses the severity of liver disease with a maximal score of 15. The three scores evaluated are those usually reported[28,29] namely Pugh A (≤ 6), B (7–9), and C (10–15). The Shaw score has been designed to identify risk of death within 6 months of OLT. The scoring system was developed from a multivariate analysis of preoperative risk factors and perioperative blood loss. The maximal score is 9, and the ranges used are those proposed by Shaw et al.[30] They are low risk— 0–3 points, intermediate risk—4–6 points, and high risk—≥ 7 points.

For each scoring system, the odds ratio (OR) and 95% confidence intervals are presented in Table 6. Because almost all patients had at least one grade 1, 2, and 2a complication, risk factors for these types of complications were evaluated for the development of at least two of each of these complications. For grade 2b to 4b complications, patients were studied according to the presence or absence of respective complications. Again, grade 1 to 3 complications were evaluated excluding all patients who died or were retransplanted within 3 months of transplantation, and grade 4 complications were evaluated excluding patients who died from recurrence of the liver disease within 3 months of their transplant. Statistical significance was achieved when the 95% confidence interval of the OR does not include the value 1.0.

No scoring system accurately predicted grade 1 or 2 complications. APACHE II score was the best predictor of grade 3, 4, and 3–4 complications, and the Shaw score correlated with grade 4 and 3–4 complications.

Other Risk Factors

Potential risk factors for the development of complications after first OLT were investigated. The risk factors studied (and percent of patients with the respective factors) were as follows: sex of the donor/recipient: female/female (15.1%), female/male (19.5%), male/male (31.4%), and male/female (34%); donor age: < 40 years (70.5%), 40–60 years (26.7%), >60 years (2.9%); donor morbid obesity (body mass index [BMI]) >30 kg/m^2 (4.3%); donor ≥ 5 days on a respirator (15.7%); donor cardiac arrest (1.4%); donor serum bilirubin > 50μmol/L (29mg/L) (2.2%); donor aspartate aminotransferase (AST) > 100 IU/L (8.1%); donor prothrombin time > 15 sec (6.3%); and cytomegalovirus donor/recipient status: negative/negative (15.1%), negative/positive (32.3%), positive/negative (12.2%), and positive/positive (40.4%). Recipient risk factors studied were age < 40 years (28.6%), 40–60 years (57.6%), >60 years (13.8%); medical status of listing: 1–2 (82.3%) *versus* 3–4 (17.7%); etiology of liver disease (Table 2); previous abdominal surgery (54.3%); previous shunt surgery (9.5%); portal vein thrombosis (14.8%); documented history of spontaneous bacterial peritonitis (39%). Technical factors directly related to the transplantation procedure were use of Eurocollins (21%) *versus* UW (79%) cold preservation solution; cold ischemia time in UW group ≥ 12 hrs (5.7%); rewarming time ≥ 90 minutes (21.4%)—i.e., time the

Table 6. PREOPERATIVE PROGNOSTIC SCORES RELATED TO COMPLICATIONS

		Type of Complication				
	No.* of Patients	≥ Two Grade 1† Complications	≥ Two Grade 2 Complications	Grade G3 Complications	Grade 4 Complications	Grade 3 or 4 Complications
Apache II						
9–12 points	53–71*	0.8 (35): 0.3–1.7†	1.4 (44): 0.6–3.5	*3.7 (22): 1.6–8.9*	1.5 (29): 0.7–3.3	2.0 (41): 1.0–4.1
≥13 points	42–61	0.8 (28): 0.3–1.9	1.2 (34): 0.5–3.2	*2.9 (15): 1.2–7.4*	*2.7 (25): 1.3–5.78*	4.2 (39): 2.1–8.2
Pugh						
7–9 points (B)	50–61	1.1 (36): 0.4–3.1	*3.7 (43): 1.2–11.6*	1.5 (14): 0.5–4.7	1.2 (15): 0.4–3.5	1.8 (29): 0.9–3.5
≥10 points (C)	84–118	0.8 (55): 0.3–2.1	2.7 (69): 1.0–7.5	1.9 (28): 0.6–5.6	1.9 (40): 0.7–5.0	1.6 (67): 0.8–3.3
Shaw						
4–6 points	49–72	0.6 (30): 0.3–1.2	2.9 (44): 1.0–8.2	1.1 (15): 0.5–2.4	*2.6 (26): 1.3–5.3*	*1.9 (41): 1.0–3.4*
≥7 points	20–34	0.7 (13): 0.2–1.9	1.3 (10): 0.4–4.3	1.4 (7): 0.5–3.9	*4.6 (17): 2.0–10.7*	*2.9 (23): 1.3–6.7*

* First number is the number of patients used for analysis of grade 1–3 complications, i.e., excluding patients who died or were retransplanted within 3 months of transplantation. The second number is the number of patients used for analysis of grade 4 and 3–4 complications, i.e., only excluding those who died from recurrence of the liver disease within 3 months of their transplant.

† Odds Ratio (number of patients): 95% confidence interval of the OR is presented for each grade of complications. All scores are compared with the respective low scores. Statistically significant values are indicated in italics.

liver was removed from the cold until reperfusion through the portal vein; Roux-en-Y choledochojejunostomy (23.3%) *versus* choledocho-choledocho anastomosis (76.7%).

Univariate (Fisher's exact test and logistic regression) and multivariate (stepwise logistic regression) analyses of risk factors and scoring systems related to complications were evaluated (Table 7). Multivariate analysis was performed using only significant factors in the univariate analysis. Another multivariate analysis with all factors also was performed, but failed to identify any new risk factors, and most of the factors in the previous analysis were no longer significant.

Few statistically significant risk factors were identified. Donor obesity was the only significant risk factors for developing two or more grade 1 complications. In the multivariate analysis, Pugh score and rewarming time of the liver were associated independently with grade 2 complications. Medical status 3 to 4 was predictive of grade 2 complications, and high APACHE II score was predictive of grade 2b complications. APACHE II was independently predictive of grade 3, 4, and 3–4 complications. The only other independent predictive factor for grade 4 complications was donor cardiac arrest.

DISCUSSION

In this study, we proposed definitions of negative outcomes and a classification of complications by severity for solid organ transplantation. The application of this proposal to liver transplantation has enabled us to differentiate the rate of failure to cure from complications and has provided a practical and meaningful analysis of the incidence of specific complications by severity. The classification also has allowed us to show a decrease in the incidence of mild (grade 1) and life-threatening (grade 2) complications over time, which was related partially to a better medical status of patients at the time of transplantation. Finally, individual preoperative risk factors and three prognostic scoring systems for prediction of grades of complications were evaluated.

Health care evaluation has become increasingly important in our society. A major shortcoming in this task is the lack of standard methodology to measure quality of care.[31,32] In 1989, the U.S. Congress established the Federal Agency for Health Care Policy and Research to support research on outcomes of medical interventions and on the development of guidelines.[33] Research on outcome of solid organ transplantation is of particular interest because of the cost of this intervention and the shortage of donors. Objective data on patient outcome would permit the identification of risk factors for poor outcome and allow allocation of donor organs to the most suitable recipient. Defined outcome measures also will be a valuable tool in prospective studies of new therapies.

In evaluating an intervention such as organ transplantation, the first step is to determine whether the intervention is effective—i.e., whether it eradicates the disease. This proposed definition of negative outcome differentiates failure to cure—i.e., recurrence or persistence of the primary disease—from complications. An intervention with a high incidence of failure to cure does not require further investigation. For example, liver transplantation for chronic hepatitis B had an 86% recurrence rate

Table 7. UNIVARIATE (FISHER'S EXACT TEST AND LOGISTIC REGRESSION) AND MULTIVARIATE (STEPWISE LOGISTIC REGRESSION) ANALYSIS OF RISK FACTORS ASSOCIATED WITH INCREASED INCIDENCE OF COMPLICATIONS

	Univariate Analysis	Multivariate Analysis
Grade 1	Donor obesity (p = 0.02)	Donor obesity (p = 0.02)
Grade 2	Recipient listing status 3-4 (p = 0.05)	
	Pugh score B and C (p = 0.04)	Pugh score B and C (p = 0.04)
	High donor bilirubin (p = 0.05)	
	Use of Eurocollins solution (p = 0.05)	
	Rewarming ischemia time >90 min (p = 0.03)	Rewarming ischemia time >90 min (p = 0.05)
Grade 2a	Status 3-4 (p = 0.05)	Status 3-4 (p = 0.05)
	Pugh scores B and C (p = 0.02)	
	Rewarming ischemia time >90 min. (p = 0.05)	
Grade 2b	Recipient listing status 4 (p = 0.05)	
	Shaw score ≥7 (p = 0.02)	Shaw score ≥7 (p = 0.05)
	Choledocho-choledocho anastomosi's (*vs.* Roux-en-Y choledochojejunostomy) (p = 0.03)	
	Rewarming ischemia time (p = 0.05)	
Grade 3	APACHE II score 9-12, and ≥13 (p < 0.01)	APACHE II score 9-12, and ≥13 (p < 0.01)
Grade 4	Recipient listing status 4 (p = 0.05)	
	APACHE II score >12 (p = 0.03)	APACHE II score >2 (p = 0.03)
	Shaw score ≥7 (p <0.01)	
	Donor cardiac arrest (p = 0.001)	Donor cardiac arrest (p = 0.01)
	Cold ischemia time >12 hr (p = 0.05)	
	CMV donor positive/recipient negative (p = 0.03)	
Grade 3-4	APACHE II score ≥13 (p = 0.01)	Apache II score ≥13 (p = 0.02)
	Shaw score ≥6 (p = <0.01)	
	Donor cardiac arrest (p = 0.04)	

Risk factors associated with ≥ two grade 1, 2, and 2a complications, respectively, and with at least one grade 2b, 3, and 4 complications are presented.

and a 30% mortality rate at 1 year. Thus, OLT is not recommended for this disease until new approaches are identified. In this study, failure to cure was presented in three basic categories—patient alive, retransplantation, and death. There is a need for finer gradation systems. Patients with recurrent hepatitis who are asymptomatic with only serologic markers should be differentiated from those disabled with cirrhosis or end-stage liver disease. Perhaps, a classification similar to that proposed for complications should be developed to assess the severity of failure to cure.

We must emphasize that our classification of complications is a proposal, whose aim is to stimulate discussion that could lead to a consensus and a common method of reporting complications. The ultimate goal is to obtain a comprehensive and standardized way of reporting all negative outcomes of transplantation. The use of mild *versus* severe, life-threatening, or major complications in some series has not added much to the knowledge of the morbidity in transplantation because in most instances, no definition is given for the terminology used. Reporting by diagnosis also gives no information about the severity of the complications. For instance, postoperative pancreatitis may range from a mild form requiring no specific treatment (grade 1), to the development of abscess requiring percutaneous drainage or surgery (grade 2b), to residual diabetes (grade 3) or death (grade 4b). A classification of complications suitable for comparison with other therapies, among different centers and over time, should be based on defined criteria to provide interpretable and reproducible information. Our proposed classification system is based on the principle of severity as indicated by the intervention necessary to treat the complications. In designing this system, we tried to keep the definitions as objective and simple as possible.

However, because any classification of this type requires separations based on somewhat arbitrary criteria, a multidisciplinary consensus conference may be the best way to achieve general agreement. From such a conference, it also might be worthwhile to attempt to weigh the respective grades of complications to derive a score representative of overall morbidity. In prospective studies of new therapies, a morbidity score would be a much more sensitive outcome measure than mortality alone. Finally, once agreement on a classification system is achieved, it will be important to test the interobserver variability in grading complications. For instance, this

can be done by presenting several cases to physicians and nurses for gradation of complications. In our study, all complications of OLT were graded independently by two authors (PAC and CAC), and interobserver variability was less than 2% (data not shown).

In designing a classification of complications, a balance between the extent of subclassification and the use of the classification system is an important consideration.[5] Less subclassification leads to groups with a broad range of members, and members at the extreme ends of a group do not seem to belong in the same category. More subclassification reduces this problem but makes the system difficult to use. Furthermore, multiple subgrouping reduces the size of each group and increases the risk of type 2 errors. However, the use of a standardized subclassification system would facilitate meta-analysis of large numbers of patients. In this way, analysis of the subgroups could be retained, and valid correlation to risk factors made.

The application of the definition of negative outcomes and classification of complications in the first 215 OLT indicated a 13.5% rate of failure to cure and a 99.1% complication rate. Thus, if we were looking at morbidity as a whole, we would report an almost 100% incidence of complications, but we would have no information about the severity of complications. Most patients had grade 1 and 2 complications, about 20% had grade 3 complications, and 30% had grade 4 complications. Presenting complications by severity does not preclude analysis of complications by general diagnosis, as usually is reported.[34] In fact, the classification allowed better comparison of the relative severity of specific complications. Acute rejection was the most common grade 1 complication (69.2% of the total of patients), but was seldom the cause of permanent graft injury (grade 3) or graft loss (grade 4); infection was usually more serious, representing the major cause of grade 2 complications (64.2%) and the major grade 4 complication (13.8%). Primary dysfunction was a grade 2 complication in approximately one fourth of patients and usually did not extend the ICU stay significantly (grade 2a). However, PDF was the second most common cause of grade 4 complications. Renal failure was the most common grade 3 complications at 1 year. Most frequent indications for retransplantation (grade 4a) were PDF (2.9% of the total of patients), hepatic artery thrombosis (2.3%), and rejection (1.9%). Death (grade 4b) was associated mainly with sepsis (13.8%) and PDF (8.1%).

This standardization of outcome also has allowed comparisons of results over time. A decrease in all types of complications reaching statistical significance for overall, grade 1, and grade 2 complications was noted. The fact that the initial patients were at higher risk than the latter patients, according to the medical status, suggests that improvement was related partially to better selection of patients. Improvement in patient management, such as the use of UW solution and shorter rewarming time of the donor liver, also may have been an important factor.

This classification of complications has allowed us to study risk factors related to different degrees of morbidity. The preoperative APACHE II score appeared to be the best predictor of grade 3,4, and 3–4 complications. Of course, validation of APACHE II score in OLT requires prospective investigation. Others have found that postoperative APACHE II score computed within 24 hours after OLT had no value in predicting death.[35] As previously reported,[11,36,37] other factors, such as rewarming time of the donor liver > 90 minutes and donor obesity, were identified as risk factors in the multivariate analysis. Again, further prospective studies are necessary to identify significant risk factors for the respective grade of complications. Previous studies assessing risk factors in OLT[2–4,11,38–40] have used only mortality or specific complications, such as infection or PDF, as endpoints, irrespective of the severity, because no gradation system for morbidity was available. This proposed classification also would enable us to identify risk factors associated with specific complications by severity (e.g., grade 1 rejection, grade 2 infection, etc.). This is being done, but it is not the purpose of this study to present in detail an analysis of risk factors associated with all specific complications.

We have presented definitions of negative outcomes and a classification of complications after solid organ transplantation. The use of the classification in OLT has allowed us to better appreciate the morbidity of the procedure, show improvement in the number of some complications, analyze risk factors, and test some prognostic scoring systems. This evaluation of outcome was performed from a medical perspective. Evaluation from a patient perspective—i.e., quality of life and patient satisfaction—also must be considered, and standardization in this area also is desirable. General agreement on a standardized way of reporting outcomes is of paramount importance for obtaining conclusive results and for designing guidelines of treatment. Patients, physicians, health care administrators, and society as a whole will benefit from general agreement in reporting negative outcomes.

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