

Incidence and Risk Factors for the Development of Prolonged and Severe Intrahepatic Cholestasis After Liver Transplantation

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Predictive factors for intrahepatic cholestasis after orthotopic liver transplantation (OLT) have not yet been established. We sought to identify the incidence and risk factors associated with prolonged severe intrahepatic cholestasis (PSIC) after OLT. We assessed 428 consecutive patients undergoing their first OLT. PSIC was diagnosed if a serum bilirubin concentration was greater than 100 $\mu\text{mol/L}$ and/or a 3-fold increase of alkaline phosphatase occurred within the first month after OLT and was sustained for at least 1 week in the absence of biliary complications. Multivariable logistic regression identified factors independently associated with PSIC. PSIC developed in 107 patients (25%). Independent risk factors by multivariable analysis were intraoperative transfusion of cryoprecipitate and platelets; nonidentical blood group status; suboptimal organ appearance; inpatient status before transplantation; and bacteraemia in the first month after transplantation. In contrast, acute liver failure, older age, and higher levels of serum sodium and serum potassium were all associated with a reduced likelihood of developing PSIC in the first month. There were 47 deaths in the PSIC group (44%) as opposed to 65 deaths in the non-PSIC group (20%) after OLT. A poor preoperative clinical status in conjunction with a suboptimal graft was associated with PSIC after OLT. Avoidance of suboptimal livers and ABO nonidentical grafts for young patients with poor synthetic function and for pretransplant inpatients may lessen this complication and reduce the associated early mortality. *Liver Transpl* 12:1626-1633, 2006. © 2006 AASLD.

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Cholestasis can be defined as the clinical, biochemical, and histological manifestations of defective bile flow or formation. It presents with a typical biochemical pattern of raised serum bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) with relatively normal transaminases. Histologically portal tract and bile ductular inflammation is frequently accompanied by bile duct plugging and bile staining within the hepatocytes.^{1,2}

After liver transplantation, cholestasis may be extrahepatic, involving a mechanical obstruction of the main bile ducts, or intrahepatic, involving impairment of bile duct secretion because of a defect in the hepatocytes or microscopic bile ducts within the liver.³ Several etiological factors have been suggested for intrahepatic cholestasis, such as inflammation or destruction of bile

ducts,⁴ bacterial or viral infection,⁵ hepatotoxic drugs including immunosuppressives such as azathioprine,⁶ and sulfonamides used for the treatment and prophylaxis of *Pneumocystis carinii*,^{7,8} reperfusion injury, or a combination of these factors.^{6,9,10}

The pathogenesis of early intrahepatic cholestasis after liver transplantation is still unclear, and its incidence, natural history, and consequences have not been defined.¹¹ Although increases of GGT, ALP, and bilirubin are common in the immediate posttransplant period, reflecting a state of mild cholestasis, the majority of such events remain subclinical. There is, however, a group of patients who develop prolonged severe intrahepatic cholestasis (PSIC), which may be associated with irreversible liver damage requiring retransplantation.

Abbreviations: OLT, orthotopic liver transplantation; PSIC, prolonged severe intrahepatic cholestasis; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CMV, cytomegalovirus; ALF, acute liver failure; HAT, hepatic artery thrombosis. Address reprint requests to Andrew K. Burroughs, Hepatobiliary Medicine & Liver Transplant Unit, Royal Free Hospital, Pond Street, NW3 2QG London, United Kingdom. Telephone: +44-(0)20-74726229; FAX: +44-(0)20-74726226; E-mail: Andrew.Burroughs@royalfree.nhs.uk

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TABLE 1. Demographic and Clinical Characteristics of 428 Patients Included in Study

Characteristic	Total, n (%)	Prolonged severe intrahepatic cholestasis		P value
		Yes	No	
Number of patients	428 (100.0)	107 (100.0)	321 (100.0)	
Demographic factors				
Recipient sex: Male	260 (60.7)	63 (58.9)	197 (61.4)	0.73
Donor sex: Male	229 (53.5)	49 (45.8)	180 (56.1)	0.08
Recipient/donor sex mismatch	153 (35.7)	44 (41.1)	109 (34.0)	0.22
Age (yr), median (range)	49 (12–68)	47 (16–68)	50 (12–66)	0.05
Ethnic group: Caucasian	337 (78.7)	82 (76.6)	255 (79.4)	0.63
Etiology				
Hepatitis C	124 (29.0)	23 (21.5)	101 (31.5)	
Other	304 (81.0)	84 (78.5)	220 (68.5)	0.07
Recipients/donor blood group				
Identical	362 (84.8)	84 (78.5)	278 (86.9)	
Compatible	48 (11.2)	19 (17.8)	29 (9.1)	
Incompatible	17 (4.0)	4 (3.7)	13 (4.1)	0.05
Clinical factors at OLT				
Acute liver failure	41 (9.6)	15 (14.0)	26 (8.1)	0.11
Inpatient	68 (15.9)	28 (26.2)	40 (12.5)	0.001
Ventilation before OLT	26 (6.1)	9 (8.4)	17 (5.3)	0.35
Renal support before OLT	33 (7.7)	10 (9.4)	23 (7.2)	0.60
Detectable ascites	247 (57.7)	69 (64.5)	178 (55.5)	0.13
Encephalopathy before OLT	68 (15.9)	23 (21.5)	45 (14.0)	0.09
Pyrexial	13 (3.0)	2 (1.9)	11 (3.4)	0.53
Sepsis confirmed	9 (2.1)	1 (0.9)	8 (2.5)	0.46
No/limited capability for self-care	122 (28.5)	37 (34.6)	85 (26.5)	0.14

Abbreviation: OLT, orthotopic liver transplantation.

The aim of this study is to evaluate the incidence of PSIC in patients undergoing orthotopic liver transplantation (OLT), and to identify demographic and clinical factors associated with this condition.

PATIENTS AND METHODS

The study population includes all consecutive patients undergoing their first OLT at the Royal Free Hospital, London, between March 1994 and June 2002. In total, 428 patients were included in the analysis (Table 1). An additional 14 patients who underwent transplantation over this period but who died within the first postoperative week were excluded from analysis.

PSIC is defined on the basis of a serum bilirubin concentration greater than 100 $\mu\text{mol/L}$ (normal range 5–17 $\mu\text{mol/L}$) and/or a 3-fold increase of ALP (normal range 42–128 IU/L) occurring in the first month after first OLT and sustained for at least 1 week, in the absence of biliary complications.

In all cases of PSIC, an ultrasound scan was performed routinely to exclude biliary obstruction. When clinically indicated, the biliary tract was further assessed by endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, hepatic iminodiacetic acid, or computed tomographic scan. In patients with a t-tube, a cholangiogram was routinely performed. Patients with biliary complications or other causes of cholestasis, such as hemolysis,

were excluded from the evaluation of cholestasis even if they fulfilled the above-mentioned criteria for PSIC ($n = 24$).

Statistical Analysis

Factors associated with the development of PSIC were identified by χ^2 tests (for categorical variables) and Kruskal-Wallis tests (for numerical variables). Those factors associated with the development of PSIC ($P < 0.2$) in univariate models were entered into a multivariable logistic regression model by a backward selection to identify those factors independently associated with the development of PSIC. Factors were only retained in the final multivariable model if the adjusted P value was < 0.05 . All analyses were performed by the statistical package SAS, version 6.12 (SAS Institute, Cary, NC). Logistic regression analyses were performed by SAS's LOGIST procedure.

Variables Considered in the Analysis

The following variables were considered in the analysis. Donor demographics: age, sex and blood group (identical, compatible, incompatible with the recipient). Recipient demographics: age, sex, etiology of liver disease (categorized as chronic liver disease or acute liver failure [ALF]). Chronic liver disease was further categorized as hepatitis C versus non-hepatitis C-related cirrhosis).

Biochemical and hematological parameters before transplantation: hemoglobin, white blood cell count, platelets, international normalized ratio for prothrombin activity (INR), urea, creatinine, albumin, bilirubin, sodium, and potassium (all treated as continuous measurements). Pretransplantation variables: inpatient status, ventilation status, renal status, presence of fever, ascites, encephalopathy and/or history of gastrointestinal bleeding. Transplant-related factors: organ appearance, number of hepatic arteries (single/accessory), number of arterial anastomoses, type of biliary anastomosis, cold ischemia time, warm ischemia time, preservation injury, bypass time and the perioperative requirements of blood products. Infections of bacterial, fungal or viral etiology during the first 3 months; cytomegalovirus (CMV) polymerase chain reaction (PCR) testing was performed on alternate days. Initial immunosuppression and episodes of rejection were treated on the basis of protocol biopsies. Transjugular biopsies were performed routinely on day 5 postoperatively, and whenever clinically indicated to identify acute rejection. Acute rejection was scored by using the Royal Free Rejection Scoring System.¹²

After transplantation, hematological parameters and liver function tests were monitored daily. Results at days 1, 3, 7, 15, and 30 were chosen as summary measures for the purposes of this analysis. Median and ranges were calculated at each time point and have been plotted to illustrate the changing levels of the parameters in those with and without PSIC. These plots are intended for descriptive purposes only. The trends in the 2 groups are expected to differ because of the nature of our definition and the known correlates between the biochemical markers. Thus, we have not tested the difference in trends for statistical significance.

RESULTS

A total of 428 patients were included in the analysis. One hundred and seven patients (25.0%) fulfilled the definition of PSIC, 16 patients on the basis of both a raised bilirubin and ALP, 70 patients on the basis of a raised bilirubin only, and 21 patients on the basis of a raised ALP only. Changes in levels of bilirubin, ALP, and GGT in the first month after OLT, stratified according to PSIC status, are shown in Figures 1 through 3. Overall, the incidence of PSIC has increased over time, developing in 28 (19.9%) of 141, 35 (21.6%) of 162, and 44 (35.2%) of 125 transplantations performed in 1994-1996, 1997-1999, and 2000-2002, respectively ($P = 0.007$, χ^2).

Characteristics of Patients Before or At the Time of OLT

The characteristics of the 428 patients before transplantation are listed in Table 1. Two hundred and sixty patients (60.7%) were male, and the median (range) age of patients at the time of transplantation was 49 (12-68) years. The indication for transplantation was end-stage chronic liver disease in 387 pa-

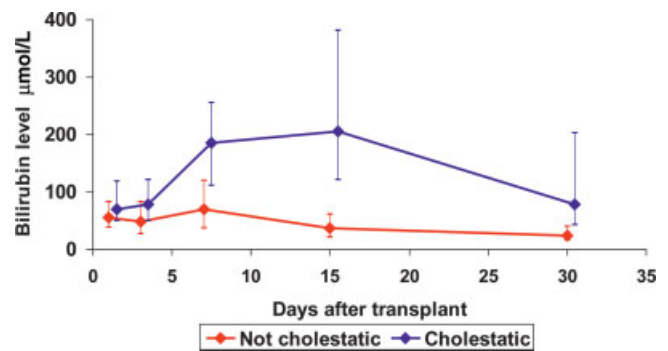


Figure 1. Bilirubin levels in the first month after OLT.

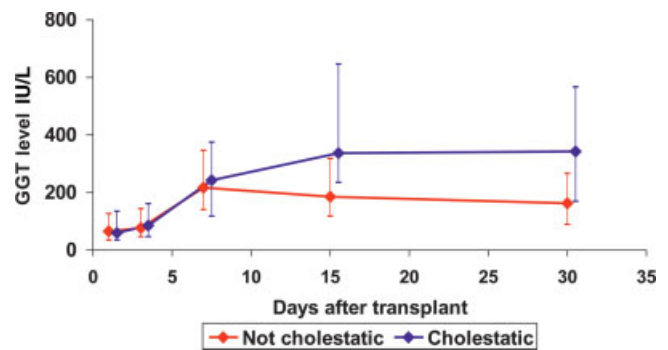


Figure 2. GGT levels in the first month after OLT.

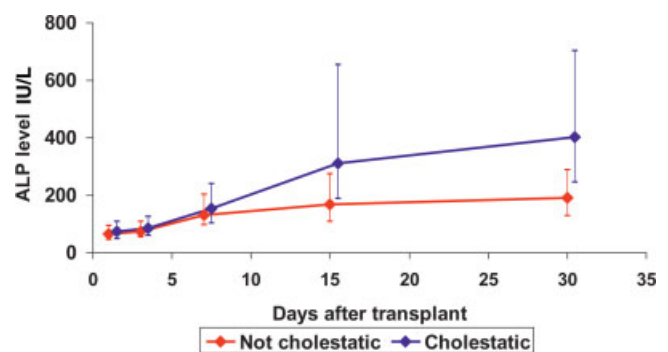


Figure 3. ALP levels in the first month after OLT.

tients (90.4%) and ALF in 41 cases (9.6%). Sixty-eight patients (15.9%) were inpatients at the time of OLT. Two hundred and forty-seven patients (57.7%) had ascites; diuretic therapy had been initiated in 276 patients (64.5%). Esophageal varices had been detected in 309 patients (72.2%); a history of variceal bleeding was present in 144 patients (33.6%); TIPPS had been performed in 35 patients (11.4%); and a surgical shunt had been placed in 4 patients (1.3%). Twenty-six patients (6.1%) required ventilatory support, and 33 (7.7%) required renal support (22 hemodialysis and 11 hemofiltration). Encephalopathy was diagnosed in 68 cases (15.9%); intracranial pressure was monitored in 6 patients (1.4%) and found to be elevated in 5 (1.2%). Thirteen patients (3.0%) were pyrexial at the time of OLT, but sepsis was confirmed

TABLE 2. Surgical Factors of the 428 Patients Included in Study

Characteristic	Total, n (%)	Prolonged severe intrahepatic cholestasis		P value
		Yes	No	
Number of patients	428 (100.0)	107 (100.0)	321 (100.0)	
Suboptimal organ appearance	53 (12.4)	20 (18.7)	33 (10.3)	0.03
Hepatic artery (donor)				
Single	337 (78.9)	85 (79.4)	252 (78.8)	
Accessory	90 (21.0)	22 (20.6)	68 (21.3)	0.99
Cold ischemia time, median (range)	662 (200-1300)	660 (206-1023)	663 (200-1300)	0.68
Bypass time, median (range)	97 (32-639)	92 (42-265)	99 (32-639)	0.91
Reperfusion time, median (range)	42 (19-106)	44 (26-85)	41 (19-106)	0.03
Biliary anastomosis, end-to-end	327 (76.4)	74 (69.2)	253 (79.1)	
Tube	78 (18.2)	28 (26.2)	50 (15.6)	
Roux-en-Y	22 (5.1)	5 (4.7)	17 (5.3)	0.05
Hepatic artery anastomosis				
Single	378 (88.3)	96 (89.7)	282 (88.1)	
Multiple	49 (11.4)	11 (10.3)	38 (11.9)	0.79
Blood products during surgery				
Blood, units				
n (%)	383 (89.5)	98 (91.6)	285 (88.8)	0.52
Median (range) units	6 (0-68)	7 (0-68)	6 (0-65)	0.02
Plasma				
n (%)	363 (84.8)	95 (83.5)	368 (88.8)	0.24
Median (range) units	5 (0-35)	7 (0-35)	5 (0-30)	0.003
Platelets				
n (%)	270 (63.2)	79 (73.8)	191 (59.3)	0.01
Median (range) units	2 (0-30)	2 (0-30)	2 (0-25)	0.04
Cryoprecipitate				
n (%)	82 (19.2)	33 (30.8)	49 (15.3)	0.001
Median (range) units	0 (0-40)	0 (0-40)	0 (0-30)	0.0004
Laboratory parameters before OLT* (normal range)				
Hemoglobin (11.5-15.5 g/dL)	11.0 (4.9-16.9)	10.6 (5.4-16.9)	11.2 (4.9-16.6)	0.002
White cell count ($3.5-11 \times 10^9/L$)	5.2 (1.3-35.4)	5.4 (1.4-25.9)	5.2 (1.3-35.4)	0.37
Platelets ($140-400 \times 10^9/L$)	77.5 (13-1085)	74 (13-414)	78 (13-1085)	0.36
Urea (3.0-6.5 mmol/L)	5.1 (0.7-36.3)	5.1 (0.7-36.3)	5.1 (0.7-30.3)	0.98
Creatinine (60-97 $\mu\text{mol/L}$)	87 (34-623)	88 (34-623)	87 (48-601)	0.53
Albumin (35-50 g/L)	32 (8-51)	31 (20-49)	33 (8-51)	0.02
International normalized ratio for prothrombin activity (0.9-1.2)	1.5 (0.8-16.2)	1.6 (0.9-14)	1.5 (0.8-16.2)	0.008
Bilirubin (5-17 mol/L)	50 (3-1135)	69 (6-986)	43 (3-1135)	0.003
Serum sodium (135-145 $\mu\text{mol/L}$)	136 (120-159)	136 (121-149)	137 (120-159)	0.10
Serum potassium (3.5-5.0 $\mu\text{mol/L}$)	4.1 (2.2-6.7)	4.0 (2.2-6.5)	4.1 (2.7-6.7)	0.03

Abbreviation: OLT, orthotopic liver transplantation.

*All continuous variables are expressed as median and range.

in only 9 cases (2.1%) (positive culture from sputum in 3 patients, blood culture in 1, urine in 1, ascitic fluid in 1, and from other sources in 2).

Transplant Details

Transplant details are shown in Table 2. Graft appearance was judged as suboptimal in 53 cases (12.4%). The presence of steatosis was essentially based on the duty surgeons' assessment of the graft, and suboptimal appearance refers to mildly or moderately fatty livers because severely steatotic organs were not used. Cold ischemia time ranged from 200 to 1300 minutes (me-

dian 662 minutes). An accessory hepatic artery was found in 90 donors. During transplantation, 383 patients (89.5%) required blood transfusion (median 6 units, range 0-68), 363 patients (84.8%) received fresh frozen plasma (median 5 units, range 0-35), 270 patients (63.2%) received platelets (median 2, range 0-30), and 82 patients (19.2%) received cryoprecipitate (median 0, range 0-40).

Postoperative Details

Postoperative details are shown in Table 3. CMV infection (diagnosed by 2 consecutive positive blood samples

TABLE 3. Posttransplant-Related Factors of the 428 Patients Included in Study

Characteristic	Total, n (%)	Prolonged severe intrahepatic cholestasis		P value
		Yes	No	
Number of patients	428 (100.0)	107 (100.0)	321 (100.0)	
Infections posttransplant				
Cytomegalovirus*	65 (15.2)	23 (21.5)	42 (13.1)	0.05
Fungal	19 (4.4)	5 (4.7)	14 (4.4)	1.00
Chest	159 (37.1)	44 (41.1)	115 (35.8)	0.39
Bacterial	71 (16.6)	26 (24.3)	45 (14.0)	0.02
Urinary tract infection	22 (5.1)	4 (3.7)	18 (5.6)	0.61
Abdominal	61 (14.3)	20 (18.7)	41 (12.8)	0.18
Wound	80 (18.7)	24 (22.4)	67 (17.5)	0.30
Other	79 (18.8)	23 (21.7)	56 (17.8)	0.46
Initial immunosuppression				
Day 3: Prednisolone	244 (57.0)	50 (46.7)	194 (60.4)	0.02
Azathioprine	233 (54.4)	49 (45.8)	184 (57.3)	0.05
Cyclosporine	139 (32.5)	24 (22.4)	115 (35.8)	0.02
FK 506	259 (60.5)	72 (67.3)	187 (58.3)	0.12
MMF	6 (1.4)	4 (3.7)	2 (0.6)	0.04

*Defined as 2 consecutive blood samples on alternate days as PCR CMV-DNA positive.

for CMV DNA by PCR) was documented in 65 cases (15.2%), bacteraemia in 71 (16.6%), and fungal infection in 19 cases (4.4%). Sepsis was a common complication and was primarily due to chest (37.1%) and wound (18.7%) infections.

Immunosuppression on day 3 after OLT is shown in Table 3. In the PSIC group, 60 patients (56%) had at least one episode of treated rejection, and in the non-PSIC group, 169 patients (52.7%) had at least one episode of treated rejection.

There were 47 deaths (44%) in the PSIC group—27 were in the first 3 months after transplantation, 7 between 3 and 12 months, and the remaining 13 more than 12 months after OLT. In the non-PSIC group, 65 deaths (20%) occurred—21 in the first 3 months, 17 between 3 and 12 months, and 27 more than 12 months after OLT ($P = 0.03$, χ^2). Retransplantation was performed in 8 patients with PSIC (7.5%) (3 for hepatic artery thrombosis [HAT], 2 for primary graft nonfunction, 2 for recurrent disease, and 1 for chronic rejection), and in 32 patients in the non-PSIC group (10%).

Factors Associated With the Development of PSIC in Univariate Analyses

In terms of demographic factors considered (Table 1), univariate analyses showed that those developing PSIC were more likely to be younger ($P = 0.05$) and with a compatible blood group ($P = 0.05$) than those who did not develop PSIC. In addition, those developing PSIC were less likely to have a male donor ($P = 0.08$) and less likely to have an etiology of hepatitis C ($P = 0.07$) than those who did not develop PSIC. However, these differences were only of borderline significance. There were no relationships between the development of PSIC and recipient sex, donor-recipient sex, mismatch, or ethnic-

ity. Patients with PSIC were more likely to be an inpatient at the time of OLT than those who did not develop PSIC ($P = 0.001$). In addition these patients were also more likely to have signs of encephalopathy ($P = 0.09$), but there were no associations in the univariate analyses between the development of PSIC and any other clinical factors before transplantation.

Among the transplant-related factors (Table 2), the development of PSIC was associated with a suboptimal liver appearance ($P = 0.03$), the type of biliary anastomosis performed ($P = 0.05$), and the amount of blood ($P = 0.02$), fresh-frozen plasma ($P = 0.003$), platelets ($P = 0.04$), and cryoprecipitate ($P = 0.0004$) received during surgery. A longer warm ischemia time was also associated with the development of PSIC ($P = 0.03$). Pretransplantation laboratory parameters associated with the development of PSIC included lower hemoglobin ($P = 0.002$), lower albumin ($P = 0.02$), higher INR ($P = 0.008$), higher bilirubin ($P = 0.003$), and lower potassium ($P = 0.03$) levels.

Postoperative factors identified (Table 3) included a diagnosis of CMV infection ($P = 0.05$) or bacteraemia ($P = 0.02$) after transplantation, and the type of immunosuppression received at day 3, particularly prednisolone ($P = 0.02$), azathioprine ($P = 0.05$), cyclosporin ($P = 0.02$), and mycophenolate mofetil ($P = 0.04$).

Factors Associated With the Development of PSIC in Multivariable Analyses

All variables associated with the development of PSIC in the univariate analyses with a significance value of $P < 0.2$ were included in a multivariable logistic regression model to identify the factors that were independently associated with the development of PSIC. This model identified 10 factors that were independently associ-

TABLE 4. Factors Independently Associated With Development of Prolonged Severe Intrahepatic Cholestasis (Multivariable Logistic Regression Analyses)

Factor	Odds ratio	95% Confidence interval	P value
Inpatient status before OLT	3.22	1.31-7.94	0.01
Bacteraemia during first 30 days after OLT	2.77	1.48-5.18	0.002
Compatible blood group vs. others	2.08	1.02-4.22	0.04
Suboptimal organ appearance	2.12	1.06-4.23	0.03
Platelets requirement during OLT	1.76	1.02-3.05	0.04
Cryoprecipitate requirement during OLT	1.05	1.00-1.10	0.05
Serum sodium (per unit higher)	0.95	0.90-1.00	0.04
Age at OLT (per 5 yr older)	0.88	0.78-0.98	0.02
Serum potassium (per unit higher)	0.61	0.39-0.96	0.03
Acute liver failure	0.19	0.06-0.63	0.007

Abbreviation: OLT, orthotopic liver transplantation.

ated with the development of PSIC (Table 4). The factors that were associated with increased odds of developing PCIS were inpatient status at the time of OLT (odds ratio [OR] 3.22, $P = 0.01$), suboptimal organ appearance (OR 2.12, $P = 0.03$), platelet (OR 1.76, $P = 0.04$), or cryoprecipitate transfusion (OR per additional unit, 1.05, $P = 0.05$) during surgery, compatible blood group with that of the donor (as opposed to identical or incompatible blood groups) (OR 2.08, $P = 0.04$), and bacteraemia during the first month of follow-up (OR 2.77, $P = 0.002$). In contrast, ALF (OR 0.19, $P = 0.007$), older age (OR per 5 years older 0.88, $P = 0.02$), and higher levels of serum sodium (OR per unit higher 0.95, $P = 0.04$), and serum potassium (OR per unit higher 0.61, $P = 0.03$) were all associated with reduced odds of PSIC in the first month. The model did not substantially change quantitatively when subjects with acute cellular rejection or those solely with a raised ALP were excluded.

DISCUSSION

An increase in serum concentrations of bilirubin, ALP, and GGT occur quite commonly after liver transplantation resulting in postoperative cholestasis, which in the majority of cases remains subclinical. This study evaluated the presence of a less common clinical condition characterized by the presence of a prolonged and severe intrahepatic cholestasis, as indicated by a bilirubin greater than 100 $\mu\text{mol/L}$ and/or a 3-fold increase of ALP occurring in the first month after OLT and sustained for at least 1 week. GGT was not used as a test despite correlating well with bilirubin and ALP, because it had been shown in this analysis to be insufficiently specific in selecting patients with cholestasis. The cut-off parameters to define cholestasis were designed to exclude patients with only minimal biochemical abnormalities. In Figures 1-3, a clear distinction between patients with and without high bilirubin is shown without any overlap between the 2 populations, and even with regard to ALP and GGT, the 2 curves do not converge within 30 days after OLT.

In our series, 25% of patients developed PSIC,

whereas cholestasis was documented in 40% and 53% of cases in 2 previous studies.^{11,13} In these studies, cholestasis was defined as a 48 hours or more increase of bilirubin or liver enzyme levels, or failure of these levels to show progressive improvement after transplantation. In addition, no specific mortality was reported in these studies.¹¹ The lack of a uniform definition makes it difficult to assess the real incidence of post-OLT cholestasis, and the lower rate in this study is likely the result of the strict inclusion criteria used to define this syndrome.

Our analysis aimed to correlate perioperative variables with the development of PSIC. Infection, bacterial or fungal, is known to occur in up to 70% of OLT patients in the first month after transplantation.¹⁴ We found that only bacteraemia was associated with PSIC in the multivariable analysis ($P = 0.002$). A correlation with CMV infection, which can produce a cholestatic picture commonly in the first 3 months after OLT,¹⁰ was also demonstrated ($P = 0.05$) in the univariate analysis. However, this did not remain significant in the multivariable analysis. In our center, CMV infection is monitored by alternate-day PCR testing, and preemptive therapy is instituted if 2 consecutive blood samples are positive. This treats infection early and prevents disease,¹⁵ and may explain the lack of correlation with CMV infection found in other studies.^{16,17}

Regarding etiologies of liver disease, we considered only hepatitis C separately, because fibrosing cholestatic hepatitis is a rare but well-known form of hepatitis C recurrence that can present with cholestasis early after OLT.^{18,19} In hepatitis C patients, PSIC was diagnosed less frequently, although this observation was not statistically significant ($P = 0.07$).

Cholestasis after liver transplantation due to drug administration is difficult to assess. Analyzing the literature from kidney transplantation suggests that the use of cyclosporin, azathioprine, and even tacrolimus is associated with the development of cholestasis.^{6,7,11} In this study, the administration of either cyclosporin or

azathioprine, but not tacrolimus, was associated with severe cholestasis ($P = 0.02$ and $P = 0.05$, respectively).

Younger recipient age and the use of suboptimal grafts correlated significantly with early postoperative PSIC. Recipient age and graft appearance have never been associated with PSIC before, and this correlation was not demonstrated in previous reports on post-OLT cholestasis.¹¹ On the other hand, graft appearance has been correlated with other forms of severe graft dysfunction. In a study on 227 OLT patients regarding primary graft nonfunction or dysfunction,²⁰ multivariable analysis identified risk factors such as severe steatosis in the graft, advanced donor age, and prolonged cold ischemia time.

Interestingly, warm ischemia but not cold ischemia time was associated with PSIC ($P = 0.03$). Ischaemia-reperfusion injury is an unavoidable injury to the allograft and is mainly due to hypothermic storage under hypoxic conditions (cold ischemia), sustained ischemia during implantation (rewarming ischemia), and restoration of blood and oxygen to the graft (reperfusion injury).¹ Of these, warm ischemia and reperfusion injury are primarily associated with marked enzyme release shortly after OLT, but a cholestatic picture may occur once transaminitis has resolved.²¹

We did not demonstrate any significant difference in the 2 groups with regard to the incidence of at least one treated episode of moderate to severe rejection (56% in the PSIC group vs. 52.7% in the non-PSIC group). There were insufficient cases of patients with multiple rejection episodes to assess if PSIC was associated with recurrent rejection.

Although ABO blood group incompatibility has been previously associated with cholestasis,²² reflecting a humoral rejection, this study has identified only the use of compatible allografts as a risk factor for PSIC. The reason for this may be that very few incompatible grafts were used, and all of these patients received plasma exchange, which may have reduced the occurrence of cholestasis. It is also interesting to note that in a recent European Liver Transplant Registry study, the use of compatible ABO compared with identical ABO livers was associated with an increased risk of mortality in both children and adult patients.²³

We excluded specific biliary problems in relation to evaluating cholestasis. Thus, not surprisingly, the multivariable analysis did not reveal the type of biliary anastomosis as being an associated factor. This study has shown that a poor perioperative patient clinical status correlates with PSIC. Hospitalized patients at the time of OLT with a low hemoglobin and albumin, high creatinine, and an abnormal INR were more likely to develop PSIC. Perioperative encephalopathy was also more frequently diagnosed in this group, although the difference did not reach statistical significance ($P = 0.09$). Unexpectedly, ALF inversely correlated with PSIC (OR = 0.19). However, ALF highly correlated with inpatient status—as by definition all these patients had been hospitalized hours or days before the liver transplant—and was found to be associated with a higher rate of PSIC in this group, although patients with ALF

were less likely to develop PSIC than patients with chronic liver disease. Of the operative parameters, transfusion of blood ($P = 0.02$), fresh frozen plasma ($P = 0.003$), platelets ($P = 0.04$), and cryoprecipitate ($P = 0.0004$) were also found to be associated with PSIC. In general, blood product transfusion reflects more severe portal hypertension associated with worse liver disease and/or suboptimal grafts with prolonged intervals to optimal correction of clotting.

Although our study was not designed to consider outcomes after PSIC, deaths within 1 year after OLT occurred in a greater proportion in the PSIC group (44%) than in the non-PSIC group (20%), suggesting that PSIC may contribute to a poorer outcome.

Retransplantation rate did not differ significantly in the 2 groups. PSIC has a less acute and dramatic presentation than other indications for urgent retransplantation such as HAT or primary graft nonfunction. Although we might have underestimated the severity of this condition, the restriction to list patients for a superurgent graft within 2 weeks from transplantation surgery is likely to have an impact on the retransplantation rate in this group of patients.

PSIC developed less frequently in patients with higher serum sodium concentration (OR 0.95). A serum sodium level greater than 132 $\mu\text{mol/L}$ seemed to act as a protective factor. Biggins et al.²⁴ studied the mortality associated with serum sodium and found that a serum sodium <126 mEq/L was a strong independent predictor of mortality.

In summary, we have set up stringent criteria to define PSIC. This is a serious and potentially lethal complication with a 44% mortality. We found that PSIC developed in younger inpatients with low serum sodium and potassium levels, which reflects a poor clinical status before transplantation. Important surgical factors are suboptimal and nonidentical grafts, and a greater platelet and cryoprecipitate requirement during surgery. Bacteraemia after OLT was also found to correlate with PSIC. All these factors are good markers of early mortality, and therefore identification of risk factors, particularly those related to recipient status, could lead to preoperative patient optimization. In practice, only certain factors, such as the donor-recipient matching and the duration of warm ischemia, can be controlled. The avoidance of suboptimal livers and ABO nonidentical grafts for younger patients and pretransplantation inpatients with poor synthetic function could be a policy that should reduce the occurrence of PSIC and perhaps its associated mortality.

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