Preoperative and Intraoperative Predictors of Postoperative Morbidity, Poor Graft Function, and Early Rejection in 190 Patients Undergoing Liver Transplantation

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Hypothesis: Preoperative and intraoperative variables predict in part adverse outcome after liver transplantation.

Design: Prospective, blinded, cohort study.

Setting: Tertiary care hospital.

Subjects: A total of 190 adult patients undergoing primary liver transplantation.

Main Outcome Measure: Adverse outcome was prospectively defined as either in-hospital death or prolonged postoperative hospitalization (>14 days) associated with morbidity. Potential preoperative and intraoperative risk factors were collected. Associations were tested by univariate analysis followed by multivariate analysis in which preoperative factors were entered before intraoperative factors.

Results: Adverse outcome occurred in 44.7% of patients. Incidences of other complications were as follows: in-hospital mortality (8.4%), primary graft nonfunction (4.2%), poor early graft function (1.1%), and early rejection (31.2%). Univariate predictors of adverse outcome were United Network for Organ Sharing status (P = .003), Child-Turcotte-Pugh score (P = .02), POSSUM physiological score (P = .002), recipient age (P = .01), preoperative serum high-density lipoprotein cholesterol level (P = .03), preoperative serum creatinine level (P = .002), preoperative serum total IgG level (P = .004), duration in hospital preoperatively (P < .001), allogeneic erythrocyte transfusions (P < .001), total intraoperative fluids (P = .002), and use of inotropic agents (P = .01). In the final multivariate model, predictors of adverse outcome were United Network for Organ Sharing status (P = .03), recipient age (P = .002), and total intraoperative fluids (P = .04). Most patients who died or had a prolonged hospitalization exhibited dysfunction of more than 1 organ system, including pulmonary, renal, and infectious complications.

Conclusions: Adverse outcome occurs frequently after liver transplantation, usually involves multiple organ systems, and is predicted in part by several preoperative and intraoperative factors.


Great strides have been made in the field of liver transplantation, and it is no longer considered an experimental procedure.1,2 Morbidity after these procedures results in suffering, prolonged hospitalization, and increased health care expenditures. Complications include acute lung injury, renal dysfunction, infection, and gastrointestinal tract dysfunction.3 Graft-related complications, such as primary nonfunction, poor early graft function, and early rejection, can result in the loss of the donor organ and may require retransplantation.

Complications after liver transplantation are likely to be multifactorial in origin. Some of the morbidity may be due to a patient’s underlying condition, for example, their preoperative renal function and United Network for Organ Sharing (UNOS) status. Morbidity after liver transplantation may also be due to intraoperative factors that affect the magnitude of the systemic proinflammatory response seen in many patients after major illness or injury.4

Previous studies of outcome after liver transplantation have been retrospective3-8 or limited to the study of a single outcome.8,7,10-12 The goal of this prospective study was to ascertain the preoperative and intraoperative predictors of the following 4 clinically relevant postoperative complications: (1) death or prolonged hospitalization associated with morbidity, (2) primary graft nonfunction, (3) poor early graft function, and (4) early rejection.
PATIENTS AND METHODS

SELECTION CRITERIA

After institutional review board approval with exemption from patient consent, 190 adult patients (aged ≥18 years) undergoing primary liver transplantation surgery were enrolled during a 17-month period at Mount Sinai Hospital, New York, NY, in a prospective blinded cohort study. Patients were excluded if they were younger than 18 years or were undergoing a repeated liver transplantation procedure. Patients were not excluded on the basis of sex, race, or ethnic group.

PROTOCOL

Study patients received routine anesthetic care and surgical management, including the routine use of prophylactic antibiotics. In addition to standard anesthesia monitors, patients had a catheter inserted into the radial artery and usually had a pulmonary artery catheter placed in the right internal jugular vein via an 8.5F sheath introducer. Acid-base status was regularly monitored by analysis of blood obtained from the radial artery catheter.

Briefly, general anesthesia was induced by means of a rapid sequence technique involving etomidate or thiopental sodium in combination with fentanyl citrate and midazolam hydrochloride. Muscle relaxation was achieved with succinylcholine chloride, followed by use of longer-acting muscle relaxants, eg, cisatracurium besylate. General anesthesia was maintained with a balanced technique consisting of fentanyl and isoflurane delivered in a mixture of air and oxygen.

The surgical procedure involved a heptectomy. Before removal of the liver, the portal vein and inferior vena cava were test clamped to predict whether the patient would remain hemodynamically stable during the anhepatic phase. Patients underwent venovenous bypass if they were hemodynamically unstable or at the discretion of the attending surgeon and anesthesiologist. In these cases, the duration of venovenous bypass was recorded.

SPECIALIZED LABORATORY ASSAYS

Gastric mucosal hypoperfusion and elevated endotoxin and proinflammatory cytokine levels have been measured in patients undergoing liver transplantation. Several previous reports have suggested that endotoxin-related serum factors may affect the degree of systemic inflammation and postoperative morbidity. Lower levels of endotoxin neutralizers, eg, lipoproteins such as high-density lipoprotein (HDL) and endogenous antiendotoxin antibodies, might be associated with better outcome on the basis of studies in other patient populations. Higher preoperative serum lipopolysaccharide binding protein (LBP) levels might reflect greater exposure to endotoxin preoperatively. Hence, assays for these factors were performed on the patients' serum as part of this protocol.

These factors were measured in residual serum from preoperative blood samples that were no longer needed by the Mount Sinai Hospital clinical laboratory. All of these serum samples were obtained preoperatively (within 72 hours before surgery) for the performance of routine chemistry tests. Blood samples were collected from patients by venipuncture into glass tubes and centrifuged, and serum was stored at −70°C until assayed according to the institution’s standard operating procedure. All laboratory measurements were performed on coded samples to blind the investigators to the patients’ identity and outcome.

Blood measurements of total cholesterol was carried out at the Iris and B. Gerald Cantor Clinical Research Laboratory of the Rogosin Institute, New York, by means of an automated clinical chemistry analyzer (Roche COBAS Integra; Roche Diagnostic Systems, Indianapolis, Ind). Total cholesterol was measured by an enzymatic method (Roche Diagnostic Systems). The HDL was measured after precipitation of β-lipoproteins with dextran sulfate and magnesium chloride.

Serum levels of LBP were quantified by enzyme-linked immunosorbent assay as previously described. Briefly, solutions containing LBP were incubated in microtiter wells coated with affinity-purified rabbit anti–human recombinant LBP (rLBP). After washing, biotin-labeled anti-rLBP was added, followed by alkaline phosphatase–labeled streptavidin and the chromogenic substrate p-nitrophenylphosphate. Levels of LBP were determined for samples and controls by interpolation from a standard curve.

Serum was tested for total IgG and IgM concentrations by laser nephelometry. The IgM and IgG antiendotoxin–core antibody levels were measured by means of an enzyme-linked immunosorbent assay described previously. Test serum samples were compared in enzyme-linked immunosorbent assay with a reference serum

RESULTS

During the 17-month study period, 227 adults underwent primary liver transplantation at Mount Sinai Hospital. A total of 190 patients were prospectively studied, and 37 patients were not studied for logistical reasons, eg, surgery occurred on a weekend or when the research coordinator was on vacation. As shown in Table 1, these 37 patients were not significantly different from the 190 patients studied with regard to age, incidence of the primary outcome variable, postoperative length of stay, and both in-hospital and 1-year mortality rates.

General perioperative characteristics (Table 2) and the indication for transplantation (Table 3) are presented for the study population. Eighty-five patients (44.7%) either died or had a postoperative hospitalization longer than 14 days associated with morbidity. For descriptive purposes only, the incidences of these complications in each of the diagnosis types are shown in Table 4. Of note, only 2 patients with a postoperative length of stay greater than 14 days had no evidence of morbidity. Pulmonary, renal, infectious, and gastrointestinal tract complications were common in patients with prolonged hospitalization.

Incidence of other complications were as follows: in-hospital mortality (8.4%), primary graft non-function (4.2%), poor early graft function (11.1%), and early rejection (31.1%). Causes of in-hospital death in the study
group were sepsis or multiple-system organ failure (n = 12), cardiac arrest (n = 2), graft failure (n = 1), and intracranial hemorrhage (n = 1). Postoperative hospital length of stay in nonsurvivors (n = 16) exhibited a mean (±SD) of 20±26 days, a median of 36 days, and a range of 10 to 14 days; associated with morbidity. Postoperative hospitalization was defined as the number of days from the day of operation (day 0) to hospital discharge. A 14-day cutoff was selected as priori for several reasons. At our hospital the care map for liver transplantation targets discharge of the patient from the hospital before the 14th postoperative day, with most patients (>50%) being discharged within 13 days of surgery. In fact, the 25th percentile for postoperative length of stay was 9 days in this cohort; hence, a 14-day cutoff represented a marked prolongation (>3 days) in the length of stay, not a trivial prolongation of 1 or 2 days that could be due to “soft factors” such as physician preference or lack of transportation. More important, by limiting this definition to patients with coexisting morbidity, these criteria excluded any patient with a prolonged hospitalization who was free of morbidity yet still in the hospital for other reasons, eg, waiting for transportation or placement.

The following 3 secondary outcomes were recorded: (1) primary graft nonfunction, defined as acute graft dysfunction necessitating retransplantation; (2) poor early graft function defined previously as a prothrombin time greater than 16 seconds on postoperative day 2 and a peak postoperative alanine aminotransferase or aspartate aminotransferase level greater than 2000 U/L; and (3) early (within the first 90 days postoperatively) histologic evidence of rejection.

STATASTICAL ANALYSIS

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study patients. A series of simple logistic regression models was used to test the univariate association between each preoperative and intraoperative factor and each of the outcomes. The resulting odds ratio estimated from these models was used to quantify that association. No adjustment was made to the nominal P value obtained from each model, since the nature of this study is descriptive. This study was not designed to provide definitive evidence about associations or the lack thereof. In addition, there is a high degree of association among the set of factors so that any adjustment based on the number of significance tests performed, such as a Bonferroni-like correction, would be unduly conservative. All of the tests performed were 2-sided.

A multiple logistic regression model was fit for the primary outcome (in-hospital death or >14-day length of stay associated with morbidity) with the use of factors found to be significantly related at the .05 level from the univariate analyses. The independent variables in this model were entered as 2 sets. The preoperative variables, as a set, were first entered into the model. Thus, the association of each preoperative variable with adverse outcome was estimated with adjustment for the other preoperative variables. The intraoperative variables were then entered into the model as a set, so that the associations they had with adverse outcome were estimated adjusted for the other intraoperative variables and also for the preoperative variables.

In this large prospective study, we observed relatively high incidences of prolonged hospitalization associated

calibrated in antienidotoxin–core antibody median units, where 100 is the median value for 1000 healthy adults’ IgG or IgM, respectively.25

DATA COLLECTION

Preoperative demographic information was collected, including indication for surgery, UNOS status, Child-Turcotte-Pugh (CTP) score, age, sex, weight, preoperative serum creatinine level, and duration of preoperative inpatient hospitalization. Intraoperative data included operative duration, duration of cold ischemia, anhepatic duration, duration of warm ischemia, duration of venovenous bypass, amounts of allogeneic blood and blood products transfused, amounts of total fluids administered intraoperatively, administration of inotropic agents, routine hemodynamic variables (eg, blood pressures, heart rate, and cardiac output), and laboratory (hematocrit and arterial blood gas analyses) variables. Although not specifically validated for liver transplantation, a preoperative physiological risk score was assigned according to the established POSSUM criteria,26 which have been recognized as being the most appropriate available score for assessing risk in noncardiac surgical patients.37 The POSSUM physiological score includes 12 preoperative factors, including age, cardiac disease, and renal function. A point value of 1, 2, 4, or 8 is assigned for 10 of the 12 factors, depending on the severity of the abnormality (eg, 1 point for no dyspnea and 8 points for dyspnea at rest), and POSSUM physiological scores can range between 12 and 88. The preoperative physiological score predicts the risk of morbidity and mortality for noncardiac surgical patients.38

OUTCOMES

The primary predefined composite end point was either in-hospital death or prolonged postoperative hospitalization (>14 days) associated with morbidity. Postoperative hospitalization was defined as the number of days from the day of operation (day 0) to hospital discharge. A 14-day cutoff was selected as priori for several reasons. At our hospital the care map for liver transplantation targets discharge of the patient from the hospital before the 14th postoperative day, with most patients (>50%) being discharged within 13 days of surgery. In fact, the 25th percentile for postoperative length of stay was 9 days in this cohort; hence, a 14-day cutoff represented a marked prolongation (>3 days)
The study of a single outcome, such as mortality, bleed-

Table 1. Characteristics of Study vs Nonstudy Patients*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Patients (n = 190)</th>
<th>Patients Not Studied (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative age, y (median)</td>
<td>54 (45-63)</td>
<td>56</td>
</tr>
<tr>
<td>Adverse outcome, No. (%)†</td>
<td>85 (44.7)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Postoperative hospital length of stay, d (median)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>In-hospital mortality, No. (%)</td>
<td>16 (8.4)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>1-y Mortality, No. (%)‡</td>
<td>34 (17.9)</td>
<td>8 (21.6)</td>
</tr>
</tbody>
</table>

*There were no significant differences (P<.05) between groups for any variable.
†Adverse outcome (primary outcome variable) represents in-hospital death or prolonged postoperative hospitalization (>14 days) with morbidity.
‡Percentage of patients who died within 1 year of surgery (includes patients who died before discharge from the hospital).

Table 2. Perioperative Patient Characteristics in 190 Patients*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 (45-63)</td>
</tr>
<tr>
<td>Sex, % M</td>
<td>59</td>
</tr>
<tr>
<td>Preoperative weight, kg</td>
<td>72 (64-87)</td>
</tr>
<tr>
<td>UNOS status, % (1/2a/2b/3)</td>
<td>7/22/47/24</td>
</tr>
<tr>
<td>Child-Turcotte-Pugh score</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>POSSUM physiological risk score</td>
<td>24 (20-29)</td>
</tr>
<tr>
<td>Time in hospital preoperatively, d</td>
<td>9 (0-19)</td>
</tr>
<tr>
<td>Preoperative serum creatinine, mg/dL</td>
<td>1.0 (0.8-1.6)</td>
</tr>
<tr>
<td>Preoperative serum LBP, µg/mL</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>Preoperative serum cholesterol, mg/dL</td>
<td>11 (82-154)</td>
</tr>
<tr>
<td>Preoperative serum HDL, mg/dL</td>
<td>25 (17-39)</td>
</tr>
<tr>
<td>Preoperative serum total IgM, g/dL</td>
<td>2.3 (1.3-4.3)</td>
</tr>
<tr>
<td>Preoperative serum total IgG, g/dL</td>
<td>22 (16-28)</td>
</tr>
<tr>
<td>Preoperative serum IgM EndoCAb, MU</td>
<td>200 (112-394)</td>
</tr>
<tr>
<td>Preoperative serum IgG EndoCAb, MU</td>
<td>281 (187-518)</td>
</tr>
<tr>
<td>Duration of cold ischemia, min</td>
<td>547 (453-706)</td>
</tr>
<tr>
<td>Duration of warm ischemia, min</td>
<td>44 (37-50)</td>
</tr>
<tr>
<td>Anhepatic duration, min</td>
<td>41 (0-56)</td>
</tr>
<tr>
<td>Intraoperative use of vein-vein bypass, %</td>
<td>22</td>
</tr>
<tr>
<td>Intraoperative use of inotropic agents, %</td>
<td>11</td>
</tr>
<tr>
<td>Intraoperative allogeneic blood, U</td>
<td>11 (6-18)</td>
</tr>
<tr>
<td>Intraoperative total fluids, L</td>
<td>7.8 (5.7-12.5)</td>
</tr>
<tr>
<td>Operative duration, min</td>
<td>495 (418-571)</td>
</tr>
<tr>
<td>Temperature at the end of surgery, °C</td>
<td>35.5 (34.8-36.2)</td>
</tr>
</tbody>
</table>

*Data are given as median (interquartile range) where appropriate. UNOS indicates United Network for Organ Sharing; LBP, lipopolysaccharide binding protein; HDL, high-density lipoprotein; and EndoCAb (MU), endotoxin core antibody level in median units. To convert creatinine to micromoles per liter, multiply by 88.4; cholesterol to millimoles per liter, 0.02586.

with morbidity, suboptimal graft function, and early rejection after orthotopic liver transplantation. Patients with prolonged hospitalization had evidence of multipletsystem organ dysfunction, with higher incidences of pulmonary, renal, and infectious complications. There were several predictors of death or prolonged hospitalization associated with morbidity. In contrast, we found few predictors of other important outcomes, such as primary graft nonfunction, poor early graft function, and early rejection.

Several previous studies of outcome after liver transplantation have been retrospective5-9 or were limited to the study of a single outcome, such as mortality, bleed-

In contrast, we found only 1 predictor each for the outcomes related to graft function, ie, UNOS status for primary nonfunction and days in hospital preoperatively for poor early graft function. One can speculate that

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predictors related to the risk of general adverse outcome, as described above, may be less important for determining graft function than some yet undetermined risk factors. Of interest, early rejection was predicted in part by lower preoperative serum low-density lipoprotein and total cholesterol levels. Although many patients had low HDL levels in the reference range, many others had abnormally low levels as manifested by a median cholesterol level of 111 mg/dL (2.9 mmol/L) (interquartile range, 82-154 mg/dL [2.1-4.0 mmol/L]). Since the new liver should have normal synthetic function, it is unclear why early rejection would be predicted by variables that reflect poor synthetic function of the replaced liver. This finding warrants further study.

Endotoxin, the lipopolysaccharide (LPS) component of gram-negative bacteria, may be an important trigger of the systemic inflammatory response syndrome in liver transplantation and other major surgical procedures. Lipopolysaccharide is toxic to humans in nanogram quantities and is found in large quantities in the human gastrointestinal tract. It can leak into the blood via an impaired gut barrier during conditions of trauma or stress. The liver normally “absorbs” LPS from the portal circulation and thus may prevent it from entering the systemic circulation under normal circumstances.

Patients undergoing liver transplantation may be at increased risk of developing LPS-mediated complications for several reasons: (1) During certain periods of the operation, eg, the anhepatic phase, patients have no functioning liver, and thus endotoxin may be more likely to move from the portal circulation into the systemic circulation. (2) Elevated endotoxin and proinflammatory cytokine levels have been measured in the blood of patients during liver transplantation. (3) Liver-derived serum factors that can potentially neutralize endotoxin, eg, HDL, may be reduced in patients with preexisting liver failure.

We measured the preoperative levels of several endogenous LPS-related factors in the blood that could be of clinical significance. These factors may play a role in the neutralization of LPS (eg, HDL) and anticore antibodies or reflect recent exposure to LPS (eg, LBP and anticore antibodies). We found that low HDL levels and extreme levels of total IgG were predictive of adverse outcome. No other preoperative LPS-related factors were associated with adverse outcome. Of note, preoperative me-
Table 6. Significant Univariate Associations Between Study Variables and Secondary Outcome Variables*  

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Graft Nonfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNOS status (1 or 2a vs 2b or 3)</td>
<td>4.40</td>
<td>1.01-19.08</td>
</tr>
<tr>
<td>Days in hospital preoperatively</td>
<td>1.02</td>
<td>1.00-1.04</td>
</tr>
</tbody>
</table>

| Poor Early Graft Function |
| Preoperative serum cholesterol (per 10-mg/dL increase) | 1.04 | 1.01-1.08 | .02 |
| Preoperative serum LDL (per 10-mg/dL increase) | 1.05 | 1.01-1.10 | .03 |
| Duration of cold ischemia, h | 0.86 | 0.77-0.96 | .01 |
| Operative duration, h | 0.85 | 0.72-0.99 | .04 |

| Early Rejection |
| Preoperative LBP level | 2.07 | 1.77-2.43 | <.001 |

*OR indicates odds ratio; CI, confidence interval; UNOS, United Network for Organ Sharing; and LDL, low-density lipoprotein.

dian anti-LPS antibody levels in liver transplant patients were 2- to 3-fold higher than the median for healthy volunteers, which suggests that these patients have long-term exposure to LPS. Similarly, some patients appeared to have had a recent exposure to LPS, as evidenced by high LBP levels before surgery, although the LBP levels were lower on average than those found in patients with documented sepsis and gram-negative bacteremia.

Nevertheless, a normal preoperative LBP level does not rule out exposure to LPS, since LBP is synthesized in the liver and most of these patients had abnormal liver function before surgery.

Our study has 2 limitations. First, any prospective cohort study such as ours can demonstrate associations between variables but cannot prove a causal relationship. Second, our results reflect the experience of a single medical center and thus may not be generalizable to other settings. A study by Edwards et al reported that low-volume centers (<20 procedures per year) had higher mortality rates than high-volume centers (>20 procedures per year). The 1-year mortality rate for our study population of 17.9% (n=190) is extremely similar to the 1-year mortality rate of 18.2% (n=995) reported by Edwards et al for affiliated centers performing more than 20 transplant procedures per year. These data suggest that the findings at our high-volume center (>150 transplants per year) are probably generalizable to other high-volume centers. It is also reasonable to speculate that the incidences of other adverse outcomes noted in our study may be higher in low-volume centers than in our setting.

Although mortality rates have improved after liver transplantation, adverse outcomes still occur frequently. Postoperative morbidity usually involves multiple organ systems and is predicted in part by several preoperative and intraoperative factors.

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From the Departments of Anesthesiology (Dr S Bennett-Guerrero and Feierman and Ms Winfree) and Surgery (Dr Sheiner), Mount Sinai School of Medicine, New York, NY; Department of Medical Microbiology, University of Edinburgh Medical School, Edinburgh, Scotland (Dr Barclay); Department of Biostatistics, Columbia University School of Public Health, New York (Dr Parides); Centre for Anaesthesia, University College London Hospitals, London, England (Dr Mythen); Rogosin Institute, Rockefeller University, New York (Drs Levine and Parker); and XOMA (US) LLC, Berkeley, Calif (Dr Carroll and Mr White). Dr Bennett-Guerrero is now with the Department of Anesthesiology, Columbia University College of Physicians & Surgeons.

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