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ORIGINAL ARTICLE

Postoperative complications as a predictor for survival after liver transplantation – proposition of a prognostic score

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Abstract

Background: Liver transplantation is major surgery with a high risk of complications. Existing scoring systems for evaluating complications after surgery are not specific for liver transplantation. Nor are they designed to evaluate the relation to recipient survival or graft loss. We wished to uncover the relation between postoperative complications and one-year risk of death or retransplantation, and to develop a prognostic score for complications based on our findings.

Method: The study was a retrospective cohort study including 253 adult liver recipients. Thirty-days postoperative complications were registered using the Clavien-Dindo classification. A prognostic score was developed based on types, severity, and quantity of complications.

Results: A total of 1113 complications occurred in 233 (92.1%) of the patients. One-year mortality or graft loss was associated with graft, biliary, surgical, systemic, pulmonary, cardiovascular, renal, and infectious complication but not with neurologic or gastrointestinal complications. The developed score was more accurate in predicting the outcome than both the modified Clavien-Dindo score and the Comprehensive Complication Index.

Conclusion: Types, severity, and quantity of different postoperative complications after liver transplantation are not equally important. The proposed score may focus attention on treating or preventing complications with strong relation to recipient mortality or graft loss.

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Introduction

In the field of liver transplantation long-term mortality and risk of graft loss has not improved significantly over the last decades.[1,2] Focus of research has mainly been preoperative risk factors.[3–7] Little attention has been given to the postoperative course and the complications following liver transplantation.

Postoperative complications occurring within 30 days after major surgery are associated with reduced long-term survival.[8,9] Liver transplantation is complex and extensive surgery with a high risk of complications[10,11] which lead to increased risk of mortality and graft loss.[12]

Complications after general surgery[13] and hepatic surgery[14–16] including liver transplantations[10] can be scored using the Clavien-Dindo (CD) classification. Research is limited and to our knowledge no studies have examined the prognostic importance of all complications after liver transplantation combined in respect to the type (e.g. graft related, biliary, surgical, etc.) and severity. Classifications allow for uniformity in reporting results and scoring systems may be used to evaluate the importance of various complications, which in turn may improve clinical practice. However, existing scoring systems are not specific for liver transplantation, nor are they related to recipient or graft survival.[17,18] Therefore, a scoring system to assess prognostic importance of type, severity, and quantity of postoperative complications, may provide a useful tool to improve clinical practice in the postoperative course.

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We hypothesized that the type and severity of a given complication is related to recipient mortality or graft loss. Furthermore, that accumulation of multiple complications adds to the risk. We aimed to explore this by 1) identifying all complications occurring within 30 days after transplantation, 2) relate the complication type, severity, and quantity to risk of one-year recipient mortality or graft loss, 3) develop a scoring system for complications according prognostic importance, 4) compare this scoring system with a modified Clavien-Dindo score and the Comprehensive Complication Index, and 5) test the score for independence of surgical, donor, and recipient specific risk factors.

Method

Study design, population, and variables

The study was a retrospective cohort study including all adult liver recipients transplanted in Denmark from 2011 to 2016. Patients were identified by a unique personal social security number. Patients entered at date of transplantation and were followed for one year, until retransplantation, death, or March 14th 2017, whatever came first. Patients were only eligible once, thus excluded when retransplanted. We evaluated all postoperative complications occurring within 30 days after transplantation and the endpoint was one-year recipient mortality or graft loss.

Confounding risk factors with respect to the recipient, the donor and the surgical procedure have been widely investigated. Two generally accepted models have identified factors of important prognostic significance; the Model for End-stage Liver Disease (MELD) score[4] and the Eurotransplant Donor Risk Index (ER-DRI).[7] By adjusting for these, the score was tested for independence of surgical (cold ischemia time), recipient specific (bilirubin, International Normalized Ratio (INR), creatinine, and pretransplant dialysis), and donor specific (age, cause of death, split liver donation, and allocation) risk factors. Gamma glutamyl transpeptidase levels included in the ET-DRI were not obtainable and thus excluded.

All postoperative complications were recorded from medical records. Complications were defined as any deviation from the normal postoperative course.[16] All complications were registered according to the Clavien-Dindo classification, a simple classification showed to be reproducible and able to increase uniformity in reporting complications. The classification is based on the severity and treatment needed to handle the complication. Complications can be classified as grade 1 (no need for treatment (with few pharmacological exceptions)), grade 2 (required pharmacological treatment, including transfusion and parenteral nutrition), grade 3a or b (required surgical, endoscopic, or radiological intervention (not under (a)/under (b) general anesthesia)), grade 4 a or b (life threatening single (a) or multiple (b) organ dysfunction (inclusive CNS complications)), or grade 5 (death).[13] Grade 1–2 complications are considered mild while grade 3–5 are considered severe. Prior to data collection, all possible postoperative complications described in the literature[11,19–21] were evaluated by a liver transplantations expert (AR) and either classified as complications or accepted as part of the normal postoperative course following liver transplantation. Certain minor abnormalities in the postoperative course, which may be considered complications after less extensive surgery, are expected events after liver transplantation and are thus not considered complications. For example, electrolyte imbalance was only considered a complication if clinically treated as a grade 2 or higher. A complete list of inclusion and exclusion criteria for potential complications can be found in supplementary material 1. Complications found during data collection were continuously evaluated in the same manner. In the initial stage seven cases were cross checked to insure uniformity in registering complications. Finally complications were grouped according to their type (graft related, biliary, surgical, systemic, infectious, neurologic, pulmonary, cardiovascular, gastrointestinal, renal, or other complications).

Study data were managed and stored using REDCap electronic data capture tools hosted at Center of Excellence for Health, Immunity and Infections (CHIP), Rigshospitalet, University of Copenhagen.[22] The study was approved by the Danish Data Protection Agency (2012-58-0004) and Danish Patient Safety Authority (3-3013-1948-1). The STROBE guidelines for cohort studies were followed reporting this study.

Statistics

COX regression analysis was used to examine the relation between each type of postoperative complication and recipient mortality or graft loss. Due to the sample size it was not possible to perform multiple regression analysis without losing to much strength of the included variables. For this reason, the correlation was analyzed with univariate COX regression analysis. This was done in three steps by examining the effect of 1) any complication (yes/no), 2) each complication, and 3) each of a certain severity. All three steps were performed with all types of complications. Based on the results we computed a score to assess the total complication burden for a patient following transplantation. All relevant HRs were transformed with natural logarithm to enable addition. The score is expressed by the exponential function of this summation (i.e. exp [ln (HR 1) + ln (HR 2) + ln (HR n)]).

When examining low frequency covariates, the risk of type I errors increases. Lagishetty and Duffull have estimated the covariate frequency associated with type 1 error value of 0.05 to be around 50%, 20%, and 10% with sample sizes of 20, 100, and 1 000, respectively.[23] Based on these findings, we accepted a cut-off frequency of 15% with our sample size of 253 recipients. Thus, covariates needed to occur a minimum 38 times to be analyzed. Therefore, we could only analyze differences in severity in graft related, biliary, surgical, and pulmonary complications. For the same reason complications registered as 'other' could not be

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