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ORIGINAL ARTICLE

Early identification of patients at increased risk for hepatic insufficiency, complications and mortality after major hepatectomy

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Abstract

Objective: Total bilirubin (TB) of >7 mg/dl is an accepted definition of postoperative hepatic insufficiency (PHI) given its association with the occurrence of complications and mortality after hepatectomy. The aim of this study was to identify a surrogate marker for PHI early in the postoperative course.

Methods: A single-institution database of patients undergoing major hepatectomy (three or more segments) during 2000–2012 was retrospectively reviewed. Demographic, clinicopathologic and perioperative factors were assessed for their association with PHI, defined as postoperative TB of >7 mg/dl or new ascites. Secondary outcomes included complications, major complications (Clavien–Dindo Grades III–V) and 90-day mortality.

Results: A total of 607 patients undergoing major hepatectomy without bile duct reconstruction were identified. Postoperative hepatic insufficiency occurred in 60 (9.9%) patients. A postoperative day 3 (PoD 3) TB level of ≥3 mg/dl was the only early perioperative factor associated with the development of PHI on multivariate analysis [hazard ratio (HR) = 7.81, 95% confidence interval (CI) 3.74–16.31; $P < 0.001$]. A PoD 3 TB of ≥3 mg/dl was associated with increased risk for postoperative complications (75.7% versus 53.9%), major complications (45.6% versus 17.6%), and 90-day mortality (15.5% versus 2.3%). This association persisted on multivariate analysis for any complications (HR = 1.98, 95% CI 1.10–3.54; $P = 0.022$), major complications (HR = 3.18, 95% CI 1.90–5.32; $P < 0.001$), and 90-day mortality (HR = 8.11, 95% CI 3.00–21.92; $P < 0.001$).

Conclusions: Total bilirubin of ≥3 mg/dl on PoD 3 after major hepatectomy is associated with PHI, increased complications, major complications and 90-day mortality. This marker may serve as an early postoperative predictor of hepatic insufficiency.

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Introduction

Improvements in patient selection, perioperative management, cross-sectional imaging and surgical techniques in liver resection have led to increases in both the indications for hepatectomy and the number of operations performed. Once as high as 20%, mortality rates after major hepatectomy have recently been reported to be as low as 1.3%.[1–5] Although it is not a frequent occurrence, postoperative hepatic insufficiency (PHI) is a devastating complication that remains a major cause of post-hepatectomy mortality.[3,6,7]

In the last decade, in excess of 50 studies have sought to define post-hepatectomy liver failure.[2,8–11] Many authors incorporate

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postoperative serum bilirubin values and the international normalized ratio (INR) in their definitions; others consider clinical conditions, such as hepatic encephalopathy or ascites, and still others use a combination of the two.[2,12,13] The timing of the measurement of these variables in the postoperative period is also inconsistent: some studies measure at 4, 5 and 7 days postoperatively, whereas others describe merely the presence of a particular variable at any time-point. For example, the '50–50 criteria' utilize both bilirubin level and INR on postoperative day 5 (PoD 5) as predictors of post-hepatectomy mortality. By contrast, Hyder *et al.* proposed a comprehensive algorithm for predicting PHI after hepatectomy.[4] One of the most commonly accepted and simplest definitions of PHI is a peak total serum bilirubin of >7 mg/dl in the postoperative period.[2] Regardless of which definition of PHI is applied, all of them are limited by the fact that in most patients PHI is not identified until late in the postoperative course. An early predictor of PHI and adverse outcomes would be helpful to identify at-risk patients. The aim of this study was to identify a simple and early postoperative predictor of subsequent hepatic insufficiency and other adverse outcomes, including complications and early mortality, after major hepatectomy.

Materials and methods

Institutional review board approval for this study was obtained and the protocol was conducted in accordance with the Health Insurance Portability and Accountability Act of 1996. All patients who underwent major hepatectomy, defined as the resection of three or more anatomical liver segments, between January 2000 and July 2012 were identified from a prospectively maintained, single-institution database. Patients who underwent biliary reconstruction and those for whom bilirubin data were inadequate were excluded from this study.

A complete review of medical records was performed. Basic demographic and clinicopathologic data were collected and recorded in the database, as were preoperative and postoperative relevant laboratory values, operative details and outcomes. Individual total bilirubin levels and INR were recorded on PoDs 1–5. When multiple values were available for a single 24-h period, the highest value was recorded as the value for that time period. Peak postoperative total bilirubin and INR for up to 30 days postoperatively were recorded.

The study objective was to identify a predictor of PHI early in the postoperative period. The primary outcome was PHI, specifically defined as a peak postoperative bilirubin level of >7 mg/dl and/or the presence of new ascites.[2,14] Secondary outcomes included any complication, major complications defined as those of Clavien–Dindo Grades III–V, and 90-day all-cause mortality.[15]

All demographic, clinicopathologic and operative data were assessed for significant relationships with PHI using the chi-squared or Fisher's exact tests for categorical variables and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, as appropriate. Variables associated with PHI were identified on univariate analysis; those found to have a statistically significant association ($P < 0.05$) were included in a multivariate logistic regression to assess independent correlation. Receiver operating characteristic (ROC) curve analysis was performed to identify the total bilirubin level in the early postoperative period that was best associated with the subsequent development of PHI. Once this value was identified, univariate and multivariate models were constructed for each secondary endpoint. Finally, demographic and pre- and intraoperative clinicopathologic variables were analysed for their associations with the early postoperative bilirubin level that best predicted PHI. A *P*-value of < 0.05 was considered to indicate statistical significance.

Results

Of the 751 patients who underwent major hepatectomy at Emory University Hospital during 2000–2012, 144 (19.2%) patients underwent concomitant biliary reconstruction and were consequently excluded from this study. Of the remaining 607 patients, 535 (88.1%) had sufficient data on total bilirubin levels available for analysis. Demographic, clinicopathologic and perioperative data are summarized in Table 1. The cohort included 443 patients (73.0%) with a diagnosis of cancer, of which the most common indication for operation was colorectal liver metastasis ($n = 232$, 52.4%). The mean ± standard deviation (SD) preoperative total bilirubin level was 0.7 ± 0.65 mg/dl.

Sixty patients (11.2%) met the criteria for PHI. Postoperative complications occurred in 352 patients (65.8%) and major complications (Clavien–Dindo Grades III–V) occurred in 125 (23.4%). The 90-day mortality rate was 5.0% ($n = 27$) and the readmission rate was 17.4% ($n = 93$).

To identify an early postoperative indicator of PHI, an ROC curve was constructed (Fig. 1) to ascertain the early postoperative bilirubin level best associated with PHI. Bilirubin levels for the first 3 days postoperatively were analysed and that for PoD 3 revealed the best fit curve [area under the curve (AUC): 0.85]. A PoD 3 bilirubin value of ≥3 mg/dl had the strongest association with the subsequent development of PHI, with sensitivity of 60% and specificity of 86%. The positive predictive value of PoD 3 bilirubin of ≥3 mg/dl for the development of PHI was 33.0% (34 of 103 patients), and the negative predictive value was 94.0% (406 of 432 patients).

On univariate analysis, several demographic and preoperative variables were found to be significantly associated with PHI, including older age, male gender, cancer diagnosis, low preoperative albumin, a preoperative Model for End-stage Liver Disease (MELD) score of ≥8, and a preoperative tissue diagnosis of cirrhosis. Perioperative variables that significantly increased the risk for progression to PHI were higher intraoperative estimated blood loss (EBL), requirement for intraoperative blood transfusion, fresh frozen plasma (FFP) transfusion before PoD 2,