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ORIGINAL ARTICLE

Factors associated with fatal liver failure after extended hepatectomy

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Abstract

Background: Posthepatectomy liver failure (PHLF) is the leading cause of posthepatectomy mortality. This study aimed to revisit the etiology and pattern of PHLF and its role in posthepatectomy morbidity and mortality.

Methods: The pattern and etiology of PHLF and subsequent morbidity and mortality were analysed in the subgroup of patients without cirrhosis undergoing an extended hepatectomy (≥4 segments) over a 5 year period. PHLF was defined using ISGLS criteria and/or 50-50 and/or peak serum bilirubin >7 mg/dl.

Results: Among 285 included patients (median age 62 [20–89]), 81 (28%) developed PHLF with higher rates of major complications (38%) and mortality (27%) than patients without PHLF (13% and 2%, respectively; $p < 0.001$). Twenty-six patients (9%) died, 22 of whom had PHLF. Of these 22 patients, only 4 patients died from complications purely-attributed to PHLF. All the remaining 18 patients had additional peri-operative factors that contributed to the mortality of which severe vascular events were the most common.

Conclusion: PHLF is associated with higher rates of morbidity and mortality following extended resection. The etiology of PHLF is multifactorial with vascular events being common precipitant. The multifactorial origin of PHLF may explain the low predictive value of current clinical risk scores.

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Introduction

In the era of multimodal treatment, new surgical techniques, such as extended or two-stage hepatectomy, have the potential to offer long term survival in patients with primary or metastatic liver tumours previously considered unresectable.[1–3] Currently the primary reason precluding hepatic resection for patients with isolated primary or secondary hepatic malignancy is the volume of the remnant liver (RLV) rather than the number or distribution of the malignancy.[4–6] As the extent of resections has increased, "small-for-size" syndrome and "post-hepatectomy liver failure" (PHLF, i.e. hyperbilirubinemia, coagulopathy, encephalopathy, refractory ascites and death from sepsis) have been described, generally resulting from the reduction of liver mass below a certain threshold.[4] Thus, the probability of developing PHLF increases in patients once the volume of the remnant liver parenchyma drops below 25% of the total liver volume in patients with normal parenchyma (or 0.5% of body weight),[7] or below 30% or 40% in patients with reduced parenchymal function such as in the case of steatosis, cirrhosis or previous exposure to multiple cycles of chemotherapy.[4,8] The treatment of PHLF is limited and therefore, PHLF remains the leading cause of post-hepatectomy death, occurring in up to one third of PHLF patients.[9–11] Postoperatively, a clinically-relevant definition of PHLF able to distinguish a moderate, reversible complication from a more serious, life-threatening complication remains problematic. In a previous study of the main PHLF definitions, the 50-50 criterion[12] of PHLF has been shown to be the most powerful predictor of major morbidity and 90-day liver-related mortality although the sensitivity was very low.[13] The aim of this study was to revisit the origin and pattern of PHLF and its role in postoperative morbidity and mortality in a large single centre cohort of patients.

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Patients and methods

An analysis of a prospectively-completed computerized database recording all consecutive hepatic resections from a single center between January 2007 and December 2012 was performed. To focus on patients more likely to develop PHLF due to an insufficient hepatic remnant and ensure a homogenous cohort of patients only those who underwent an extended hepatic resection (≥4 segments) without underlying cirrhosis were included for further analysis. Selection criteria for hepatic resection included adequate patient fitness for surgery and preservation of sufficient functional liver parenchyma as defined by RLV ≥25% or 0.5% of the body weight according to CT volumetry.[6,7,14] Portal vein embolization (PVE) was performed 3–8 weeks before hepatectomy in patients with estimated RLV less than 25% of the total liver volume (40% in case of preoperative jaundice, severe steatosis >30% or fibrosis ≥F2) or 0.5% of the body weight. In event of failure to reach an adequate future RLV patients did not proceed to surgery. Patients were considered as having received preoperative chemotherapy when they had systemic treatment within three months prior to hepatic resection, considering this is the length of time needed for drugs to exert their deleterious effects over normal hepatic tissue.[15]

Hepatic resection

Surgical technique of liver resection and different methods of vascular control to reduce intraoperative bleeding have been described elsewhere.[6,16] Concomitant procedures performed at the time of major hepatectomy were recorded, in particular vascular and/or biliary reconstructions and major extrahepatic procedures. For each resected specimen, an experienced pathologist performed a specific histological analysis of representative sections of non-neoplastic hepatic parenchyma. Fatty accumulation was considered pathologic when the hepatic fat content involved 30% or more of hepatocytes.[17] Liver fibrosis was quantified according to the METAVIR score[18] using Sirius red stained sections: absent (F0), portal fibrosis without septa (F1), portal fibrosis with rare septa (F2), and numerous septa (F3) (exclusion of F4 fibrosis).

Postoperative assessment and care

In all patients, liver function tests were sampled routinely on postoperative days (POD) 1, 3, 5, and 7 and as clinically indicated thereafter. Postoperative morbidity and mortality were recorded prospectively. Special emphasis was placed on the occurrence of PHLF defined according to one or more of the following definitions: the International Study Group of Liver Surgery classification[19] (i.e. increased International Normalized Ratio (INR) with concomitant hyperbilirubinemia at POD5 or after according to the normal limits of the local laboratory), the "50-50" criteria (i.e. prothrombin time (PT), expressed as a percentage of the normal level of prothrombin activity <50% with concomitant hyperbilirubinemia >50 μmol/L at POD5 or after)[12] and/or a peak serum bilirubin >7 mg/dl ("PeakBili >7").[10] Postoperative morbidity and mortality were defined as complication(s) and/or death within 3 months after surgery or before discharge from hospital and graded according to the Clavien–Dindo classification.[20] The primary endpoint was postoperative mortality related to PHLF itself or to multisystem organ failure including PHLF.

Statistical analysis

Continuous variables were expressed as the median [ranges] and were compared using the Mann–Whitney test or Wilcoxon test for paired samples. Categorical variables were expressed as percentages and compared using χ^2 or Fisher exact tests, as appropriate. All analyses were performed using SPSS, version 22.0 (SPSS, Chicago, IL). The significance threshold was set to $P < 0.05$.

Results

Study population

During the study period 795 patients underwent hepatic resection of whom 285 (36%) met inclusion criteria. Baseline patient characteristics are summarized in Table 1 and perioperative data

Table 1 Clinicopathological characteristics of the study population (n = 285)

	Patients
Age (years)	62 [20–89]
Gender	
Male	169 (59%)
Female	116 (41%)
BMI (kg/m^2)	25.2 [16.6–40.3]
ASA class	
ASA 1	43 (15%)
ASA 2	181 (63%)
ASA 3	61 (21%)
Preoperative biliary drainage	26 (9%)
Preoperative portal vein embolization	66 (23%)
Preoperative bilirubinemia (mg/L)	5 [1–268]
Preoperative PT (%)	100 [60–100]
Neoadjuvant chemotherapy (within 3 months)	79 (28%)
Total number of cycles	8 [2–32]
Folfox (number of cycles)	46 (16%) (6 [2–12])
Folfiri (number of cycles)	44 (15%) (7 [2–27])
Biotherapy - Avastin or Erbitux (number of cycles)	49 (17%) (6 [2–32])
Other chemotherapy (number of cycles)	11 (4%) (5 [2–21])

Results are expressed as n (%) or median [range]. ASA indicates American Society of Anesthesiologists.

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