International Surgery Journal
El-Badry AM et al. Int Surg J. 2019 Mar;6(3):648-652
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20190808

Original Research Article

Evaluation of the “50-50 criteria” of post-hepatectomy liver failure as mortality predictor after resection of liver tumors

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Received: 17 December 2018
Accepted: 30 January 2019

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ABSTRACT

Background: Post-hepatectomy liver failure (PHLF) represents a serious complication of liver resection. A standardized definition of PHLF based on serum total bilirubin (TB) level and prothrombin time (PT) reduction at the fifth postoperative day (POD-5) gained wide popularity.
Methods: Medical records of consecutive adult patients who underwent elective liver resection for hepatic neoplasms from May 2015 to April 2018 were prospectively collected. PHLF was defined as serum total bilirubin (TB) level >50 µmol and prothrombin time (PT) reduction <50% on the fifth postoperative day (POD-5). Patients with PHLF were identified as group A and compared with group B (without PHLF) regarding postoperative complications and mortality.
Results: Fifty-one patients were enrolled, forty-three with malignant (primary and secondary) neoplasms and eight with benign liver masses. Group A comprised eight patients who fulfilled the criteria of PHLF whereas 43 patients were included in group B. The mean age, gender ratio and mean number of resected liver segments were not significantly different between both groups. Patients in group A exhibited significantly increased complication rates compared with group B. Postoperative mortality occurred exclusively in group A where five among eight patients (62.5%) died postoperatively. The mortality rate was remarkably higher (100%) in cirrhotic patients who developed PHLF compared with 40% in non-cirrhotic with PHLF.
Conclusions: PHLF is associated with increased severity of postoperative complications and mortality. Development of PHLF prompts intensive treatment protocol, particularly in cirrhotic patients.

Keywords: Fifty-fifty criteria, Hepatectomy, Liver failure

INTRODUCTION

Liver resection represents the only curative treatment option for a variety of primary and secondary liver tumors.[1,2] Post-hepatectmy liver failure (PHLF) remains as serious challenge after major liver resection and may be associated with grave outcome.[3] Recognition of key factors that precisely predict poor outcome could help identification of high risk patients who would benefit from specific protective strategies or particular interventions.[4]

A major cause of PHLF is the development of small for size syndrome (SFSS) after liver resection which signifies that the remnant liver is too small to perform normal liver functions.[5] In the setting of normal liver parenchyma, SFSS relates to excessive resection of the liver parenchyma. However, in the cirrhotic, fatty and cholestatic liver PHLF develop after major liver resection due to the impaired quality of liver parenchyma.[6] Experimental studies have demonstrated that several factors are involved in the evolution of PHLF.[7] For instance, reduced platelet count was associated with slow restoration of bilirubin levels and prothrombin time after partial hepatectomy of the normal and cirrhotic liver.[8] Failure of liver regeneration is a major cause of PHLF in the fatty liver.[9]

Therefore, several definitions of PHLF which were based on bilirubin level and coagulation profile were proposed.[10,11] These definitions comprise the "50-50 criteria", the "peak bilirubin >7" rule and the hepatic damage score.[11-14] Among those systems, the simple "50-50 criteria" of PHLF as defined by Balzan and coworkers as reduction of PT by less than 50% of normal with rise of total bilirubin (TB) above 50 µmol on the fifth postoperative day (POD 5) enabled early and accurate prediction of high (>50%) mortality rate.[15]

In our center, lack of application of the standard definition of PHLF could interfere with detection of high risk patients and consequently may result in purposeless treatment delays. Therefore, we aimed at evaluation of the "50-50 criteria" as reliable predictor of mortality after liver resection.

METHODS

Medical records of consecutive adult patients who underwent liver resection from May 2015 to April 2018 at Sohag University Hospital were retrospectively reviewed.

Inclusion criteria comprised adult (>18-year-old) patients with American Society of Anesthesiologists (ASA) score of I who underwent elective liver resection for malignant and benign liver masses by the same team of surgeons. Operative procedures were applied consistently in all patients by the same surgeons. Informed consent was obtained after comprehensive explanation of planned surgical intervention from each patient.

Exclusion criteria entailed pediatric population, traumatic and emergency cases, preoperative jaundice and/or coagulopathy, and preoperative hepatic interventions, including portal vein embolization, transarterial chemo-embolization and radiofrequency ablation.

Enrolled patients were divided into two groups according to development of PHLF.[15] Group A included patients who fulfilled the "50-50 criteria" of PHLF (reduced PT by less than 50% of normal with increased TB above 50 µmol on POD 5). Group B comprised patients who have not developed PHLF.[15]

Post-hepatectomy complications were ranked according to Clavien-Dindo classification.[16] Grade I denotes need for antiemetic, antipyretics, analgesics, diuretics and electrolytes. Grade II necessitates other pharmacologic therapies and blood transfusion. Grade III requires intervention under local (IIIa) or general (IIIb) anesthesia. Grade IV mandates admission to intermediate or intensive care unit (ICU) due to single (IVa) or multiple (IVb) organ failure. Grade V indicates patient death. An overall score of postoperative complications, ranging from one to seven, was calculated for each patient through assigning one point to each of grades I, II, IIIa, IIIb, IVa, IVb and V in ascending order. The highest complication score was used to indicate the severity of complication per patient.[17] Statistical analysis was carried out by GraphPad Prism 6.0 software. Comparisons were carried out using student's t-test. For comparisons, $p<0.05$ was considered statistically significant.

RESULTS

Demographic and clinical data

Fifty-one patients (29 males), were eligible and enrolled in the study. Their age ranged from 24 to 79 (median: 44) years. Liver resection was carried out for malignant neoplasms in 43 patients and comprised hepatocellular carcinoma on top of cirrhosis (15, including one patient with repeated resection), colorectal liver metastasis (14, including 2 patients with repeated resection), non-colorectal liver metastasis (12), and intrahepatic cholangiocarcinoma (2). Eight patients underwent liver resection for benign masses, including adenoma (2), inflammatory pseudotumor (2), giant hemangioma (2), hemangioendothelioma (1), and focal nodular hyperplasia (1). Preoperative data are shown in Table 1.

Table 1: Preoperative data.

Parameter	n	%
Male gender	29	57
Smoking	17	33
Abdominal pain	45	88
Anorexia	13	25
Weight loss	11	22
Preoperative chemotherapy (CRLM)	6	12
Diabetes	11	22
Steatosis (ultrasonography)	7	14
Indication for liver resection		
Hepatocellular carcinoma in fibrosis /cirrhosis	15	29
Colorectal liver metastasis	14	27
Non-colorectal liver metastasis	12	24
Metastatic gall bladder carcinoma (10)		
Metastatic ovarian carcinoma (1)		
Metastatic breast carcinoma (1)		
Intrahepatic cholangiocarcinoma	2	4
Benign masses	8	16
Hepatocellular adenoma (2)		
Inflammatory pseudotumor (2)		
Giant hemangioma (2)		
Hemangioendothelioma (1)		
Focal nodular hyperplasia (1)		
Repeat 'second' liver resection (total = 4)		
Recurrent CRLM	2	
Recurrent metastasis from right colon carcinoma (1)		
Recurrent metastasis from rectal carcinoma (1)		
Recurrent HCC	1	

N, number of patients; % percentage of total

Intraoperative findings

Liver transection was performed using the clamp crushing technique alone in non-cirrhotic patients and in combination with the dissecting sealer in cirrhotic patients with HCC. Anatomic resection was applied in 42 patients, including 33 non-cirrhotics and 9 cirrhotics, assisted by intraoperative ultrasonography. Major resection (≥3 segments) was performed in 31 patients (61%) including 24 non-cirrhotics and 7 cirrhotics. Liver transection was performed under intermittent occlusion of the hepatoduodenal in all patients (100%) using a vessel loop as a tourniquet to induce alternating 5 and 10 minutes cycles of liver ischemia followed by reperfusion, respectively. Operative data, including values of central venous pressure and intraoperative transfusions are summarized in Table 2.

Table 2: Operative data.

Parameter	Number (%)
Technique of liver transection:	
Clamp crushing alone	36 (71)
Clamp crushing with vessel sealer	15 (29)
Anatomic liver resection:	42 (82)
Non-cirrhotics (33)	
Cirrhotics (9)	
Major Liver Resection ≥ 3 segments	31 (61)
Non-cirrhotics (24)	
Cirrhotics (7)	
Central venous pressure cm/H_2O*§	4 (1-8)
Blood loss (ml) *§	650 (280-1500)
Red blood cell transfusion (unit) *§	2 (0-5)
Plasma transfusion (units) * §	2 (0-9)

* median value, § range

Table 3: Incidence of PHLF.

Subgroup	Number
Cirrhotic	
Hepatocellular carcinoma in fibrosis /cirrhosis	3/15
Non-cirrhotic	
Colorectal liver metastasis	2/14
Non-colorectal liver metastasis	3/12
Intrahepatic cholangiocarcinoma	0/2
Benign masses	0/8
Total	8/51

Postoperative outcome

Criteria of PHLF were encountered in 8 patients (group A) and did not in the remaining 43 cases (group B). Group A included 8 patients among them there were 3 cases of hepatocellular carcinoma in cirrhotic liver, 2 patients with CRLM and 3 with non-CRLM that occurred in non-cirrhotic liver (Table 3). All patients in group A underwent major liver resection using crushing clamp technique alone in non-cirrhotic patients and in combination with the dissecting sealer in cirrhotic. The postoperative complication score was significantly higher in patients who developed PHLF (group A) compared with those who do not exhibit PHLF (group B). Likewise, the ICU and hospital stay were significantly prolonged among patients in group A compared with group B (Table 4).

Table 4: Postoperative data.

	Group A	Group B	P value
Complication score§	4 (3-7)	2 (1-3)	<0.05*
Length of hospital stay§	14 (11-35)	6 (3-21)	<0.05*
Length of ICU stay§	11 (5-18)	1 (0-3)	<0.05*

ICU, intensive care unit, *significant difference.

Prediction of in-hospital death (fifty-fifty criteria)

Postoperatively, five patients did not survive. Postoperative in-hospital death occurred exclusively in group A which showed 62.5% mortality rate (5 out of 8 patients died). Further analysis demonstrated that 100% of patients in the subgroup of HCC on cirrhosis who developed PHLF died postoperatively compared with 40% in the subgroup of patients who exhibited PHLF after colorectal and non-colorectal metastasectomy in non-cirrhotic liver (2 out of five patients died), these data are summarized in Table 5.

Table 5: Incidence of postoperative mortality after development of PHLF.

Subgroup	n.	%
Cirrhotic		
Hepatocellular carcinoma	*§3/3	100
Non-cirrhotic, malignant		
Colorectal liver metastasis	§1/2	50
Non-colorectal liver metastasis	¶1/3	33.3
Total	5/8	62.5

*cirrhosis, elderly> 65 years, ¶ preoperative chemotherapy.

DISCUSSION

In this study, we analyzed the association between PHLF defined as TB level >50 µmol and PT reduction <50% on POD-5 and postoperative mortality after liver resection at a single center. The study cohort included patients with a variety of liver masses, including HCC (in cirrhotic), CRLM and non-CRLM as well as benign swellings. PHLF developed in eight patients, among them five deaths occurred (PHLF-related mortality rate: 62.5%). Cirrhotic patients were more vulnerable to PHLF-related death compared with non-cirrhotic.

To decrease the likelihood of development of PHLF, several likely-contributing factors were considered. The method of hepatic inflow occlusion, the technique of parenchyma transection and extent of liver resection were paid most attention.

We applied intermittent liver ischemia during parenchymal transection to avoid excess blood loss. This strategy is in agreement with previous study which demonstrated that Pringle's maneuver during hepatic transection does not increase postoperative complications, particularly in the cirrhotic patients.[18]

Despite the recent studies which demonstrated that liver resection can be carried out safely under normal central venous pressure, our strategy was to maintain low central venous pressure with preservation of adequate urine output to diminish blood loss from backflow of the hepatic veins.[19]

Regarding the methods of parenchymal transection, we used the clamp-crushing technique in all transactions. This approach was in accordance with published data that show no significant difference in blood loss, complications and mortality if any of liver transection devices were used in comparison with clamp-crushing technique.[20] However, we used the vessel sealer in combination with clamp-crushing technique to safeguard against excessive blood loss in cirrhotics.

Given the likelihood of associated reduction of blood loss, anatomic resection was our preferred strategy. In particular, anatomic resection was attempted in all cirrhotic patients due to the its advantage of reduced local recurrence.[21] However, it could not be applied in all cirrhotic patients to avoid SFSS.

To explore the impact of PHLF on postoperative complications, including mortality, we used an objective and reliable system for grading of surgical complications (Clavien-Dindo system).[16,21] The complication score was significantly higher among patients who developed PHLF (group A).

In this study, 8 patients fulfilled the standard definition of PHLF as described by the "50-50 criteria".[12,22] In line with published studies, the mortality rate among those patients was extremely high. More specifically, all cirrhotic patients who developed PHLF died postoperatively (100%) compared with a mortality rate of 40% in non-cirrhotic with PHLF. This indicates an increased vulnerability of cirrhotic to postoperative death after development of PHLF.

The principal limitations of this study include the retrospective analysis and the potential for missing important data that have been obtained from relatively small subgroups. Therefore, unrecognized confounding factors cannot be excluded.

CONCLUSION

In conclusion, our results demonstrate that application of the standard definition of PHLF results in strong prediction of mortality. This should enable accurate identification of patients who need particular interventions or specific protective strategy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: El-Badry AM, Ahmed AE. Evaluation of the “50-50 criteria” of post-hepatectomy liver failure as mortality predictor after resection of liver tumors. Int Surg J 2019;6:648-52.