Risk of liver failure after major hepatectomy for patients with hepatocellular carcinoma

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Background/aims
Hepatectomies in cirrhotic patients are complex operative interventions. Extent of hepatectomy, in particular, has a direct relation to outcomes, with posthepatectomy liver failure (PHLF) being the main cause of morbidity and mortality. This work aimed to determine the frequency and the risk factors of PHLF in patients with hepatocellular carcinoma (HCC) undergoing resection of more than two segments of the liver.

Patients and methods
A retrospective study included all patients who underwent liver resection of more than two segments for HCC between 2013 and 2017. Preoperative parameters were evaluated and analyzed for their predictive value of PHLF, which was defined based on the 50–50 criteria [prothrombin index <50% (international normalized ratio >1.7) and serum bilirubin >50 μmol/l (2.9 mg/dl) on postoperative day 5].

Results
A total of 28 patients underwent liver resection of more than two segments for HCC. The mean age of patients was 58.86±8.11 years, with range between 26 and 68 years, and 68% of them were males. Hepatitis C virus infection was the most frequent etiology of liver disease followed by hepatitis B virus infection. Sixteen (57%) patients developed PHLF. Patients with PHLF had significantly higher age, lower serum albumin, and higher Child's and model for end-stage liver disease (MELD) scores. Based on multivariate regression analysis, only low serum albumin and high Child's and MELD scores were predictors for PHLF.

Conclusion
Patients with liver cirrhosis who have low serum albumin and high Child's and MELD scores who are indicated for resection of two or more liver segments have a higher risk of postresection liver failure.

Keywords:
hepatocellular carcinoma, liver cirrhosis, major resection, posthepatectomy liver failure

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Introduction

Liver failure is a serious complication that sometimes occurs after partial hepatic resection. In general, posthepatectomy liver failure (PHLF) is defined as failure of one or more of the hepatic synthetic and excretory functions including hyperbilirubinemia, hypoalbuminemia, prothrombin time prolongation, elevated lactate, and/or different grades of hepatic encephalopathy [1].

According to the so-called 50–50 criteria, PHLF is described as prothrombin index less than 50% [international normalized ratio (INR) >1.7] and serum bilirubin more than 50 μmol/l (2.9 mg/dl) on postoperative day 5. Moreover, a peak bilirubin of 7.0 mg/dl (120 μmol/l) was identified as sensitive and specific for prediction of PHLF-related death [2].

The incidence of PHLF varies between 0.7 and 9.1%. The death rate after partial hepatic resection ranged from 0 to 5%, and PHLF seems to be the main cause of mortality [3].

Residual liver volume (RLV) needed to maintain sufficient hepatic function is unknown. This is mainly dependent upon the preoperative liver status before, where RLV should be more than or equal to 25–30% in normal livers and RLV should be as high as 40–50% in liver cirrhosis. This was consistent with a good outcome after resection [4].

As most hepatocellular carcinomas (HCCs) develop on top of liver cirrhosis, the risk of PHLF is higher in this patient group. The risk also increases with decrease in RLV. So major resections are only justifiable in a very selected group of patients, who are sometimes beyond the guidelines [5].

So this work was designed to determine the frequency and the risk factors of PHLF after major resection in patients with HCC on top of liver cirrhosis.

Patients and methods

All patients with HCC on top of liver cirrhosis who were managed by liver resection of two or more segments in the period between January 2013 and January 2017 at Al-Rajhi Assiut University Liver Hospital were included.

Recording of medical history and all laboratory investigations, including complete blood count, liver function tests, serum creatinine, blood urea, and coagulation profile, including the INR at the baseline (preoperative) and fifth-postoperative day, where PHLF is considered according to 50–50 criteria, was done.

Other data were collected as preoperative imaging studies, including abdominal ultrasonography and triphasic multislice computed tomography abdomen ±dynamic MRI with diffusion. Operative details such as blood transfusion, vascular resection, segment resected, and volume resected were included. Approval of the study from the local ethics committee was obtained. All patients were consented for data to be used in the current study.

Statistical analysis

Data were collected and analyzed using statistical package for the social science (version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean±SD or median (range), whereas nominal data were expressed in the form of frequency (percentage).

χ^2 test was used to compare the nominal data of different groups in the study, whereas Student *t* test was used to compare the mean of different groups. Multivariate regression analysis was used to evaluate the independent predictors of PHLF. Level of confidence interval was kept at 95%, and *P* value was significant if less than 0.05.

Results

Mean age of included patients was 58.86±8.11 years, with range between 26 and 68 years. Overall, 68% of the patients were males, and hepatitis C virus (HCV) infection was the most frequent etiology of liver disease followed by hepatitis B virus (HBV) infection.

Based on 50–50 criteria, 16 (57%) patients developed PHLF. So the studied patients were subdivided into subgroups according to the development of PHLF. Group I included those patients who developed PHLF (*n*=16), and group II included those patients who did not develop PHLF (*n*=12).

There were no significant differences between patients who developed PHLF and those who did not regarding most baseline characteristics, except age, as the mean age of patients who developed PHLF was significantly higher than those who did not develop PHLF (60.30±7.89 vs. 57.10±8.18, *P*=0.02) (Table 1).

No significant difference was found between both groups regarding baseline laboratory data with the exception of serum albumin, which was significantly lower in group I (33.55±5.7 mg/dl) when compared with group II (38.23 ±5.03 mg/dl, *P*=0.03). All patients in group I had significantly higher Child's and model for end-stage liver disease (MELD) scores in comparison with group II (5.44±0.41vs. 5.08±0.36, *P*=0.01 and 9.24 ±1.36 vs. 7.11±1.03, *P*=0.03, respectively). It was also noticed that albumin–bilirubin (ALBI) score had insignificant difference between both the groups (Table 2).

Table 1 Demographic data of both groups

Variables	Group I (*N*=16)	Group II (*N*=12)	*P* value
Age (years)	60.30±7.89	57.10±8.18	0.02
Sex			0.91
Male	11 (68.7)	8 (66.7)	
Female	5 (31.3)	4 (33.3)	
Residence			0.69
Rural	13 (81)	9 (75)	
Urban	3 (19)	3 (25)	
Economic status			0.23
Low	10 (62.5)	10 (83.3)	
High	6 (37.5)	2 (16.7)	
Etiology of liver cirrhosis			0.98
Hepatitis C virus	11 (69)	9 (75)	
Hepatitis B virus	4 (25)	3 (25)	
Cryptogenic	1 (6)	0 (0)	
Comorbidities			
Hypertension	4 (25)	1 (8)	0.25
Diabetes mellitus	3 (19)	3 (25)	0.93
Lung disease	1 (6)	0 (0)	0.72

Nominal data were expressed in the form of *n* (%), whereas continuous data in the form of mean±SD. *P* value was significant if less than 0.05.

Table 2 Baseline laboratory data in both groups

Data	Group I (N=16)	Group II (N=12)	P value
Liver function tests			
Bilirubin (μmol/l)	18.67 ±1.99	14.12 ±2.03	0.55
Direct bilirubin (μmol/l)	7.5±2.13	6.98±0.99	0.11
Serum albumin (mg/dl)	33.55±5.7	38.23 ±5.03	0.03
Alanine transaminase (U/l)	52.09 ±10.11	54.68 ±13.22	0.46
Aspartate transaminase (U/l)	63.01 ±17.13	66.01 ±12.67	0.99
Kidney function tests			
Blood urea nitrogen (mg/dl)	5.79±1.42	4.48±1.55	0.09
Serum creatinine (mg/dl)	69.02 ±15.88	65.48 ±17.11	0.17
Complete blood count			
Total leukocytic count (×10^6/ml)	7.02±2.70	5.73±1.73	0.13
Hemoglobin (g/dl)	13.05 ±2.04	13.34 ±1.47	0.59
Platelets (×10^6/ml)	119.14 ±35.21	145.6 ±55.87	0.21
Prothrombin time (s)	12.97 ±0.76	11.96 ±0.95	0.34
International randomized ratio	1.19±0.09	1.09±0.14	0.98
Prothrombin concentration (%)	80.90 ±10.15	83.33 ±9.35	0.31
Child classification			
A 5	9 (56.3)	11 (91.7)	0.04
A 6	7 (43.7)	1 (8.3)	
Child score	5.44±0.41	5.08±0.36	0.01
MELD score	9.24±1.36	7.11±1.03	0.03
Alpha feto-protein (ng/ml)	138.45 ±29.11	161.19 ±38.9	0.52
Albumin to bilirubin score (ALBI score)	−3.16 ±0.41	−3.07 ±0.47	0.55

Nominal data were expressed in the form of *n* (%), whereas continuous data in the form of mean±SD. ALBI, albumin–bilirubin; MELD, model for end-stage liver disease. *P* value was significant if less than 0.05.

Table 3 shows preoperative imaging data, intraoperative and postoperative risk factors for PHLF in both groups. A total of 25 (89.3%) patients had one hepatic focal lesion (HFL) and three (10.7%) patients had two HFLs. Ascites occurred in all patients who developed PHLF. Characteristics of HFLs on preoperative imaging had no significant differences between both groups, with the exception of mean size of HFLs, which was significantly higher in those who developed PHLF (51.09±9.87 mm^3) in comparison with those who did not develop PHLF (42.08±11.22 mm^3, P=0.00). Right hepatectomy was done in nine patients out of 28 (32%) [five in group I and four in group II], left hepatectomy in 15 (53.6%) patients, and central hemihepatectomy was done in four (14%) patients. In this study, nine (56.3%) patients needed intraoperative blood transfusion in group I compared with only two (16.7%) in group II (P=0.03).

Table 3 Preoperative imaging data and intraoperative and postoperative risk factors for posthepatectomy liver failure

Variables	Group I (N=16)	Group II (N=12)	P value
Preoperative imaging data			
Number of focal lesions			
One	14 (87.5)	11 (91.7)	0.72
Two	2 (12.5)	1 (8.3)	
Size (mm^3)	51.09±9.87	42.08±11.22	0.00
Intraoperative risk factors			
Vascular resection	3 (7.5)	2 (6.7)	0.89
Number of resected segments			
Right hemihepatectomy	5 (31.3)	4 (33.4)	0.73
Left hemihepatectomy	8 (50)	7 (58.3)	
Central hepatectomy	3 (18.7)	1 (8.3)	
Need for blood transfusion	9 (56.3)	2 (16.7)	0.03
Postoperative risk factors			
Hemorrhage	1 (6.25)	1 (8.3)	0.8
Wound infection	2 (12.5)	1 (8.3)	0.7

Nominal data were expressed in the form *n* (%) while continuous data in the form of mean±SD. *P* value was significant if less than 0.05.

Table 4 Multivariate regression analysis for predictors of posthepatectomy liver failure

Variables	Odd's ratio	95% confidence interval	P value
Age	1.98	9.19–11.03	0.08
Child score	2.11	13.2–15.94	0.02
MELD score	3.02	7.09–8.11	0.01
Size of the tumor	1.98	2.33–7.09	0.96
Serum albumin	2.99	7.98–11.03	0.00

MELD, model for end-stage liver disease. *P* value was significant if less than 0.05.

It was found that serum albumin, Child's score, and MELD score were predictors of PHLF in our study (Table 4).

Discussion

PHLF is a serious complication of major hepatic resection and occurs in up to 10% of cases [5,6]. Several studies reported a lower rate of PHLF (1–2%), but when present, it leads to high morbidity and mortality [7].

The current study included 28 patients who underwent major hepatic resection for HCC on top of liver cirrhosis, with mean age was 58.86±8.11 years. Males represented 19 (68%) patients in the study whereas females were nine (32%). HCV infection was the most frequent cause of liver disease followed by HBV infection [20 (71.4%) vs. seven (25%), respectively].

Similarly, in the study by Zaky *et al*. [8], more than 80% of the study patients were males and more than 70% of the patients were above the age of 55 years. The suggested etiology of liver cirrhosis and HCC were HCV and HBV in 56.8 and 2.7%, respectively.

A total of 16 (57%) patients in the current study developed PHLF based on criteria of the International Study Group of Liver Surgery and characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5 [9].

Advanced age (>65 years) predisposes to PHLF and postresectional mortality [10]. Elderly patients had comorbid conditions and reduced regenerative power of hepatocytes [11].

In the current study, right hepatectomy was done in nine (32%) patients, left hepatectomy in 15 (53.6%) patients, and central hemihepatectomy was done in four (14%) patients. There was no significant difference between both groups regarding characteristics of HFLs on imaging with exception of mean size of HFLs, which was significantly higher in those who developed PHLF (51.09 ±9.87 mm^3) in comparison with those who did not develop PHLF (42.08±11.22 mm^3, P=0.00).

On the contrary, Zheng *et al*. [12] screened 1683 patients with liver resection and the incidence of PHLF in their study was 2.38%. They found that hemihepatectomy with the largest resection extent led to the highest PHLF incidence (6.28%), which was significantly higher when compared with single tumor removal (1.72%). The extent of liver resection had a strong correlation with PHLF. Resection of large portions of the liver leads to increased hemorrhage and large wounds [13,14].

Ohkubo *et al.* [15] reported that survival after resection in patients with multiple HCCs was significantly shorter compared with those of patients with a single HCC. However, there was no difference in the frequency of PHLF between both groups.

The present study results detected that most of our patients had serum albumin within normal value, but it was significantly lower in those patients who developed PHLF (33.55±5.7 mg/dl) than those who did not develop PHLF (38.23±5.03 mg/dl).The present study revealed that Child's and MELD scores were predictors of PHLF in patients with liver cirrhosis and HCC (odd's ratio=2.11, P=0.02, and odd's ratio=3.02, P=0.01, respectively).

Partial liver resection is a good option in compensated cirrhosis with Child's grade A patients. Child's grade C cirrhosis is considered an absolute contraindication for hepatic resection. Most of hepatobiliary centers would consider only minor resections for Child's grade B cirrhotic patients [16].

Wang *et al*. [17] revealed that both the Child's score and the ALBI scores were independent predictors of PHLF, and the power of the ALBI score was greater than that of the Child's score, as ALBI score reflects an accurate evaluation of preoperative liver functional reserve. The ALBI score was calculated by means of the formula [$\log_{10}$ bilirubin (μmol/l)×0.66]+[albumin (g/l)×−0.0852]. The ALBI score was stratified as grade 1 (−2.60 or less), grade 2 (greater than −2.60 to less than or equal to −1.39), or grade 3 (greater than −1.39) [18]. The incidence of PHLF was analyzed in 267 patients who underwent major and 975 who had a minor liver resection. Patients with Child's score grade A had a significant low incidence of PHLF when compared with those with Child's score grade B in both major (P=0.040) and minor (P<0.001) liver resection groups. Similarly, the incidence of PHLF increased with ALBI grade (grades 1, 2, and 3) in both major (P<0.001) and minor (P<0.001) resections. In our study, ALBI score had insignificant difference between both groups, with and without PHLF.

Conclusion

In conclusion, patients with liver cirrhosis who have low serum albumin and high Child's and MELD scores who otherwise are indicated for resection of two or more liver segments have a higher risk of postresection liver failure.

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Conflicts of interest

There are no conflicts of interest.

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