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ORIGINAL ARTICLE

Post-hepatectomy liver failure after hepatic resection for hepatocellular carcinoma: a single center experience

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Abstract

Purpose Post-hepatectomy liver failure (PHLF) is one of the most feared morbidities after liver resection (LR) for hepatocellular carcinoma (HCC). We aimed to investigate the incidence and predictors of PHLF after LR for HCC and its impact on survival outcomes.

Methods We reviewed the patients who underwent LR for HCC during the period between January 2010 and 2019.

Results Two hundred sixty-eight patients were included. Patients were divided into two groups according to the occurrence of PHLF, defined according to ISGLS. The non-PHLF group included 138 patients (51.5%), while the PHLF group included 130 patients (48.5%). Two hundred forty-six patients (91.8%) had hepatitis C virus. Major liver resections were more performed in the PHLF group (40 patients (30.8%) vs. 18 patients (13%), $p = 0.001$). Longer operation time (3 vs. 2.5 h, $p = 0.001$), more blood loss (1000 vs. 500 cc, $p = 0.001$), and transfusions (81 patients (62.3%) vs. 52 patients (37.7%), $p = 0.001$) occurred in PHLF group. The 1-, 3-, and 5-year Kaplan-Meier overall survival rates for the non-PHLF group were 93.9%, 79.5%, and 53.9% and 73.2%, 58.7%, and 52.4% for the PHLF group, respectively (log rank, $p = 0.003$). The 1-, 3-, and 5-year Kaplan-Meier disease-free survival rates for the non-PHLF group were 77.7%, 42.5%, and 29.4%, and 73.3%, 42.9%, and 25.3% for the PHLF group, respectively (log rank, $p = 0.925$). Preoperative albumin, bilirubin, INR, and liver cirrhosis were significant predictors of PHLF in the logistic regression analysis.

Conclusion Egyptian patients with HCC experienced higher PHLF incidence after LR for HCC. PHLF significantly affected the long-term survival of those patients.

Keywords Post-hepatectomy liver failure · Hepatocellular carcinoma · Liver resection · Hepatitis C virus

Introduction

Hepatocellular carcinoma (HCC) is the most common malignancy affecting the liver [1]. HCC usually develops on a background of liver cirrhosis (LC) due to different causes such as chronic alcoholism, viral hepatitis, and non-alcoholic steatohepatitis [2, 3]. In Egypt, the incidence of HCC is steadily rising owing to the high prevalence of hepatitis C viral (HCV) infection (genotype 4), which is considered as the most challenging health problem by Egyptian health authorities [4].

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The management of HCC is a very challenging clinical situation. The selection of the appropriate management strategy depends on several factors including not only the tumor characteristics but also the background liver disease and the general condition of the patient. Liver resection (LR) and transplantation are the main lines of curative treatment of HCC. Owing to several limitations of liver transplantation, especially in a country like Egypt, LR remains a commonly utilized line of curative treatment for HCC patients with preserved liver functions [5, 6].

LR in the context of LC is a complex clinical situation. Despite the recent improvements in the surgical techniques and postoperative care of the patients, LR is usually associated with a high incidence of perioperative morbidities and tumor recurrence [7, 8].

Post-hepatectomy liver failure (PHLF) is one of the most feared morbidities after LR for HCC on a

background of LC [9]. The reported incidence of post-hepatectomy liver dysfunction after LR for HCC had been greatly heterogeneous among different studies [10–13]. Fukushima et al. addressed that the variations of the incidence of PHLF are related to the variations of underlying liver parenchymal disease [10]. To the best of our knowledge, no previous studies had evaluated the incidence and the impact of PHLF after LR for HCC in our locality, where HCV infection (genotype 4) is endemic.

The aim of this study is to investigate the incidence and potential risk factors of PHLF after LR for HCC. Do the performance and the outcomes of those patients significantly differ from other localities with other underlying liver diseases? Also, we aim to analyze the impact of PHLF on the long-term survival outcomes of those patients.

Materials and methods

Study design

We retrospectively review the data of patients who underwent primary LR for pathologically confirmed HCC at Gastrointestinal Surgery Center (GISC), Mansoura University, Egypt, during the period between January 2010 and January 2019. Patient data were retrieved from a prospectively maintained database for all patients undergoing LR. Patients were categorized into two groups according to the occurrence of PHLF.

Informed consent was obtained from each patient prior to surgical intervention. The study was approved by the Institutional Review Board and Local Ethical Committee at the Faculty of Medicine, Mansoura University, Egypt (Code Number: R.19.05.511).

Preoperative evaluation

Preoperative workup included detailed clinical examination, laboratory evaluation (including complete blood count, liver functions, kidney functions, alpha-fetoprotein), and radiological evaluation (including abdominal ultrasonography and triphasic computed tomography or magnetic resonance imaging).

The selection of an appropriate treatment strategy was discussed at multidisciplinary meetings. In general, LR was applied for patients with preserved liver functions (i.e., sufficient future liver remnant), without signs of severe portal hypertension, without evidence of extrahepatic metastasis, and with American Society of Anesthesiologists (ASA) grade < III [14].

Surgical procedure

The surgical procedure had been described elsewhere [15, 16]. The types of LR were defined according to Brisbane 2000 terminology [17]. LRs were classified into minor (≤ 2 segments) or major (> 2 segments) according to Couinaud classification.

Generally, parenchymal sparing LR was preferred. Major LRs were performed for patients with large tumors or tumors close to major hepatic vasculature if the future remnant liver is adequate (more than 40% of the total liver volume). The volumetric assessment was performed for selected patients requiring major liver resection with marginal liver functions. Otherwise, non-anatomical LRs were more preferred. Liver parenchymatous transection was performed by combinations of the clamp-crush method and ultrasonic devices. Intermittent Pringle's maneuver was applied selectively during liver transection. Intraoperative ultrasonography was utilized in some patients to check the resection margin and exclude the presence of multifocal tumors. Intraoperative cholangiography was performed in some patients to ensure biliostasis and assess the remnant biliary system integrity.

Postoperative care and follow-up

After surgery, patients were transferred to the intensive care unit or to the ward for monitoring of vital signs and abdominal drains. All patients underwent daily laboratory evaluation including liver functions. Abdominal ultrasonography was performed routinely in all patients. Oral fluids were started once intestinal sounds are restored. Abdominal drains were removed when daily output was less than 100 cc with the absence of any abdominal collections.

After discharge, patients were followed up in the outpatient clinic. Follow-up visit included physical examination, serum liver function tests, serum alpha-fetoprotein, abdominal ultrasonography, and triphasic computed tomography when recurrence was suspected.

Study outcomes

The primary outcome of the study is the overall incidence of PHLF, defined, and graded according to the ISGLS [18]. Secondary outcomes included the evaluation of the impact of PHLF on overall survival (OS) and disease-free survival (DFS) and also to evaluate different predictive factors for the development of PHLF after LR for HCC.

Definitions

Postoperative morbidity is defined as adverse events happening during the early postoperative period and is graded according to the Clavien-Dindo classification [19]. PHLF is defined

according to the ISGLS definition as the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which is characterized by an increased international normalized ratio and concomitant hyperbilirubinemia on or after.

postoperative day 5 [18]. PHLF is divided into 3 grades including grade A, not requiring any clinical management; grade B, requiring noninvasive management; and grade C, requiring invasive management. Postoperative biliary fistula and hemorrhage are defined according to the ISGLS definition [20, 21]. Early postoperative mortality was defined as mortality occurring during the first 90 postoperative days and was excluded from further survival analysis.

OS was calculated from the day of surgery to the day of confirmed death or the last follow-up visit. DFS was calculated from the day of surgery to the day of confirmed tumor recurrence or the day of death or last follow-up.

Statistical analysis

The Shapiro-Wilk test is used to assess the normality of continuous data. Categorical variables are expressed as number and percentage, and continuous variables are expressed as median and range. A comparison between groups is done by the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Survival analysis is performed by the Kaplan-Meier method and comparison between groups is done by the log rank test.

Univariate and multivariate analyses are done by logistic regression analysis to identify the independent risk factors for PHLF. Significant factors determined in the univariate analysis are included in the subsequent multivariate analysis.

Statistical analysis of the data is performed using IBM-SPSS software for Windows, version 24 (IBM Corp., Armonk, NY). p value < 0.05 is considered to be significant.

Results

During the study period, 268 patients underwent primary LR for pathologically confirmed HCC at Gastrointestinal Surgery Center (GISC), Mansoura University, Egypt. Patients were divided into two groups according to the occurrence of PHLF. PHLF occurred in 130 patients (48.5%), defined according to the ISGLS.

The non-PHLF group included patients without PHLF (138 patients—51.5%) and PHLF Group included patients with PHLF (130 patients—48.5%) (Fig. 1).

Demographic data

The demographic data of the study patients are shown in Table 1. Worse preoperative liver functions and higher

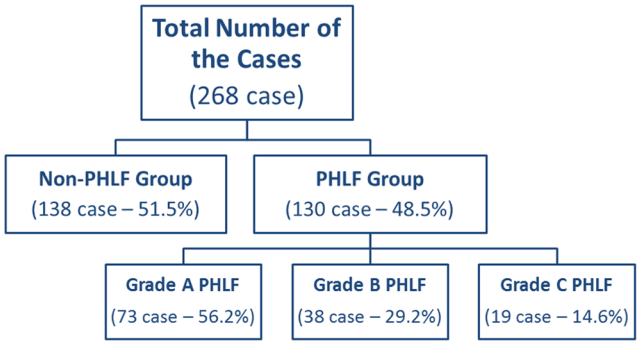

Fig. 1 Flowchart of the study patients (PHLF, post-hepatectomy liver failure)

MELD scores were noted in the PHLF group. Higher preoperative alpha-fetoprotein was noted in the PHLF group. Most of the study patients had underlying HCV infection (246 patients (91.8%)), which was significantly more in the PHLF group.

Radiological and endoscopic data are shown in Table 1. A higher incidence of radiologically proven LC was noted in the PHLF group. Also, larger tumor size was noted in the PHLF group.

Operative data

The operative data of the study patients are shown in Table 2. A higher incidence of portal vein invasion requiring portal thrombectomy was noted in the PHLF group. Major LRs were more performed in the PHLF group. Therefore, longer operation time, more blood loss, and transfusion requirements occurred in the PHLF group.

Postoperative data

Postoperative data of the study patients are shown in Table 3. PHLF occurred in 130 patients (48.5%). Most of them were grade A (73/130 patients—56.2%). Grade B occurred in 38/130 patients (29.2%) requiring diuretic therapy. Grade C occurred in 19/130 patients (14.6%) requiring radiology-guided abdominal tube drainage. Early mortality occurred in 17 patients (6.3%). All of them related to the development of PHLF and its sequences.

Pathological outcomes

Postoperative pathologic data of the study patients are shown in Table 3. A more pathologically proven LC was found in the PHLF group. Larger tumor size and higher tumor grade were found in the PHLF group. A higher incidence of microvascular and perineural invasion was found in the PHLF group.

Table 1 Demographic and radiological data of the study patients (*TACE*, trans-arterial chemo-embolization; *RFA*, radiofrequency ablation)

Variables	All cases ($N = 268$)	Non-PHLF group ($N = 138$)	PHLF group ($N = 130$)	p value
Age (years)	59 (18–78)	60 (18–77)	59 (25–78)	0.03
Gender				0.879
Male	214 (79.9%)	111 (80.4%)	103 (79.2%)	
Female	54 (20.1%)	27 (19.6%)	27 (20.8%)	
Body mass index (kg/m^2)	28.9 (17.3–42.7)	29.1 (19.6–42.7)	28.7 (17.3–40.7)	0.875
Previous TACE	18 (6.7%)	9 (6.5%)	9 (6.9%)	0.544
Previous RFA	3 (1.1%)	1 (0.7%)	2 (1.5%)	0.613
Complaint				0.26
Accidental	122 (45.5%)	66 (47.8%)	56 (43.1%)	
Pain	144 (53.7%)	70 (50.7%)	74 (56.9%)	
Mass	2 (0.7%)	2 (1.4%)	0	
Previous antiviral therapy	22 (8.2%)	11 (8%)	11 (8.5%)	1
Albumin (g/dL)	3.9 (2.1–5.3)	4 (2.2–5.3)	3.8 (2.1–5)	0.001
Bilirubin (mg/dL)	0.7 (0.3–11.2)	0.6 (0.3–2.2)	0.8 (0.4–11.2)	0.001
Alanine aminotransferase (IU/L)	40 (20–280)	40 (20–182)	41.5 (20–280)	0.108
Aspartate aminotransferase (IU/L)	50.5 (20–240)	49 (20–190)	53 (20–240)	0.027
International normalized ratio	1 (1–1.8)	1 (1–1.8)	1.1 (1–1.8)	0.001
Platelets (× 10^3/mL)	145 (34–433)	149 (44–433)	134 (34–388)	0.038
Creatinine (mg/dL)	0.8 (0.5–2.5)	0.8 (0.5–2.5)	0.8 (0.5–1.5)	0.942
Alpha-fetoprotein (ng/mL)	31 (1–2000)	18.7 (1–2000)	51 (1.5–2000)	0.01
Child-Pugh grade				0.27
A	261 (97.4%)	136 (98.6%)	125 (96.2%)	
B	7 (2.6%)	2 (1.4%)	5 (3.8%)	
Model for end-stage liver disease (MELD score)	7.5 ± 1.8	7.1 ± 1.6	7.9 ± 1.9	0.001
Hepatitis C virus	246 (91.8%)	122 (88.4%)	124 (95.4%)	0.045
Hepatitis B virus	3 (1.1%)	2 (1.4%)	1 (0.8%)	0.896
Radiological data				
Liver status				0.01
Cirrhosis	254 (94.8%)	126 (91.3%)	128 (98.5%)	
Normal	14 (5.2%)	12 (8.7%)	2 (1.5%)	
Tumor number				0.215
Single	242 (90.3%)	128 (92.8%)	114 (87.7%)	
Multiple	26 (9.7%)	10 (7.2%)	16 (12.3%)	
Tumor size (cm)	6 (1.7–20)	5.5 (1.7–18)	6.5 (2.1–20)	0.001

Survival outcomes

The median follow-up duration was 18 months (9–110). Mortality occurred in 85 patients (31.7%). The 1-, 3-, and 5-year OS rates for all study patients were 85.3%, 69.6%, and 51.7%, respectively (Fig. 2a). The 1-, 3-, and 5-year OS rates for the non-PHLF group were 93.9%, 79.5%, and 53.9%, respectively. The 1-, 3-, and 5-year OS rates for PHLF group were 73.2%, 58.7%, and 52.4%, respectively (log rank, $p = 0.003$) (Fig. 3a).

Recurrence occurred in 125 patients (46.6%). There were no significant differences between the groups regarding recurrence time, recurrence site, and recurrence management as shown in Table 4. The 1-, 3-, and 5-year DFS rates for all study patients were 75.8%, 43%, and 28.9%, respectively (Fig. 2b). The 1-, 3-, and 5-year DFS rates for the non-PHLF group were 77.7%, 42.5%, and 29.4%, respectively. The 1-, 3-, and 5-year DFS rates for PHLF group were 73.3%, 42.9%, and 25.3%, respectively (log rank, $p = 0.925$) (Fig. 3b).

Table 2 Operative data of the study patients

Variables	All cases ($N = 268$)	Non-PHLF group ($N = 138$)	PHLF group ($N = 130$)	p value
Tumor site				0.601
Right hemi-liver	135 (50.4%)	67 (48.6%)	68 (52.3%)	
Left hemi-liver	122 (45.5%)	64 (46.4%)	58 (44.6%)	
Caudate lobe	5 (1.9%)	4 (2.9%)	1 (0.8%)	
Bilobar	6 (2.2%)	3 (2.2%)	3 (2.3%)	
Tumor number				0.355
Single	248 (92.5%)	130 (94.2%)	118 (90.8%)	
Multiple	20 (7.5%)	8 (5.8%)	12 (9.2%)	
Portal vein invasion	32 (11.9%)	8 (5.8%)	24 (18.5%)	0.002
Surgery approach				0.056
Open	262 (97.8%)	132 (95.6%)	130 (100%)	
Laparoscopic	4 (1.5%)	4 (2.9%)	0	
Failed laparoscopic	2 (0.7%)	2 (1.4%)	0	
Liver resection extent				0.001
Minor	210 (78.4%)	120 (87%)	90 (69.2%)	
Major	58 (21.6%)	18 (13%)	40 (30.8%)	
Liver resection type				0.04
Tumorectomy	129 (48.1%)	79 (57.2%)	50 (38.5%)	
Segmentectomy	5 (1.9%)	2 (1.4%)	3 (2.3%)	
Left lateral sectionectomy	64 (23.9%)	32 (23.2%)	32 (24.6%)	
Right anterior sectionectomy	1 (0.4%)	1 (0.7%)	0	
Right posterior sectionectomy	1 (0.4%)	0	1 (0.8%)	
Left hepatectomy	11 (4.1%)	4 (2.9%)	7 (5.4%)	
Extended left hepatectomy	1 (0.4%)	0	1 (0.8%)	
Right hepatectomy	41 (15.3%)	13 (9.4%)	28 (21.5%)	
Extended right hepatectomy	5 (1.9%)	1 (0.7%)	4 (3.1%)	
Central hepatectomy	1 (0.4%)	0	1 (0.8%)	
Caudate lobectomy	5 (1.9%)	4 (2.9%)	1 (0.8%)	
Multiple resections	4 (1.5%)	2 (1.4%)	2 (1.5%)	
Associated portal thrombectomy	5 (1.9%)	0	5 (3.8%)	0.026
Pringle procedure use	40 (14.9%)	13 (9.4%)	27 (220.8%)	0.01
Pringle duration (min)	15 (10–45)	15 (10–30)	20 (15–45)	0.039
Operation time (h)	3 (1.2–7)	2.5 (1.2–6)	3 (1.5–7)	0.001
Blood loss (mL)	700 (100–6000)	500 (100–4000)	1000 (100–6000)	0.001
Blood transfusion	133 (49.6%)	52 (37.7%)	81 (62.3%)	0.001

Survival outcomes of different grades of PHLF

We compared the survival outcomes between different grades of PHLF patients. Mortality occurred in 16 patients (21.9%) in grade A PHLF patients, 16 patients (42.1%) in grade B PHLF patients, and in 16 patients (84.2%) in grade C PHLF patients ($p = 0.001$). The 1-, 3-, and 5-year OS rates for grade A PHLF were 90%, 65.3%, and 59.4%, respectively. The 1-, 3-, and 5-year OS rates for grade B PHLF were 65.3%, 58.3%, and 58.3%, respectively. The 1-, 3-, and 5-year OS rates for grade C PHLF were 26.3%, 14%, and 0%, respectively (log rank, $p = 0.001$) (Fig. 3c).

Recurrence occurred in 35 patients (47.9%) in grade A PHLF patients, 17 patients (44.7%) in grade B PHLF patients, and in 1 patient (5.3%) in grade C PHLF patients ($p = 0.009$). The 1-, 3-, and 5-year DFS rates for grade A PHLF were 80%, 47.4%, and 28.4%, respectively. The 1-, 3-, and 5-year DFS rates for grade B PHLF were 63.9%, 49.8%, and 41.5%, respectively. The 1-, 3-, and 5-year DFS rates for grade C PHLF were 75%, 0%, and 0%, respectively (log rank, $p = 0.737$) (Fig. 3d).

Table 3 Postoperative and pathological data of the study patients (*ICU*, intensive care unit; *US*, ultrasound; *ERCP*, endoscopic retrograde cholangiopancreatography)

Variables	All cases ($N = 268$)	Non-PHLF group ($N = 138$)	PHLF group ($N = 130$)	p value
ICU stay (days)	1 (1–22)	1 (1–6)	1 (1–22)	0.001
Hospital stay (days)	5 (2–66)	4.5 (2–66)	6 (3–53)	0.001
Morbidity	144 (53.7%)	14 (10.1%)	130 (100%)	0.001
Clavien-Dindo grade				0.061
I	58 (21.6%)	6 (4.3%)	52 (40%)	
II	46 (17.2%)	4 (2.9%)	42 (32.3%)	
III-a	11 (4.1%)	3 (2.2%)	8 (6.2%)	
III-b	10 (3.7%)	0	10 (7.7%)	
IV-a	2 (0.7%)	1 (0.7%)	1 (0.8%)	
V	17 (6.3%)	0	17 (13.1%)	
Bile leakage	15 (5.6%)	9 (6.9%)	6 (4.3%)	0.431
Bile leakage treatment				0.022
Conservative	5 (1.9%)	1 (0.8%)	4 (2.9%)	
US-guided tube	2 (0.7%)	1 (0.8%)	1 (0.7%)	
ERCP	7 (2.6%)	7 (5.4%)	0	
Operative	1 (0.4%)	0	1 (0.7%)	
Collection	14 (5.2%)	4 (2.9%)	10 (7.7%)	0.1
Collection treatment				0.195
Conservative	6 (2.2%)	2 (1.4%)	4 (3.1%)	
US-guided tube	7 (2.6%)	1 (0.7%)	6 (4.6%)	
Operative	1 (0.4%)	1 (0.7%)	0	
Internal hemorrhage	6 (2.2%)	0	6 (4.6%)	0.012
Wound infection	7 (2.6%)	3 (2.2%)	4 (3.1%)	0.716
Liver abscess	3 (1.1%)	1 (0.7%)	2 (1.5%)	0.613
Vascular complications	5 (1.9%)	0	5 (3.8%)	0.026
Respiratory complications	17 (6.3%)	5 (3.6%)	12 (9.2%)	0.079
Renal complications	4 (1.5%)	0	4 (3.1%)	0.054
Cerebral stroke	1 (0.4%)	1 (0.7%)	0	---
Ileus	1 (0.4%)	0	1 (0.8%)	---
Bleeding varices	1 (0.4%)	0	1 (%0.8)	---
Pathological data				
Tumor size (cm)	6 (1.5–20)	6 (1.5–15)	7 (1.5–20)	0.003
Tumor number				1
Single	232 (86.6%)	119 (86.2%)	113 (86.9%)	
Multiple	36 (13.4%)	19 (13.8%)	17 (13.1%)	
Resection margin				0.707
R0	237 (88.4%)	121 (87.7%)	116 (89.2%)	
R1	31 (11.6%)	17 (12.3%)	14 (10.8%)	
Capsular invasion	100 (37.3%)	56 (40.6%)	44 (33.8%)	0.259
Microvascular invasion	126 (47%)	52 (37.7%)	74 (56.9%)	0.002
Perineural invasion	108 (40.3%)	42 (30.4%)	66 (50.8%)	0.001
Tumor grade				0.007
I	49 (18.3%)	29 (21%)	20 (15.4%)	
II	153 (57.1%)	88 (63.8%)	65 (50%)	
III	57 (21.3%)	19 (13.8%)	38 (29.2%)	
IV	8 (3%)	2 (1.4%)	6 (4.6%)	
No viable tumor	1 (0.4%)	0	1 (0.8%)	
Tumor stage				0.067

Table 3 (continued)

Variables	All cases ($N = 268$)	Non-PHLF group ($N = 138$)	PHLF group ($N = 130$)	p value
T1	69 (25.7%)	41 (29.7%)	28 (21.5%)	
T2	160 (59.7%)	84 (60.9%)	76 (58.5%)	
T3	35 (13.1%)	11 (8%)	24 (18.5%)	
T4	3 (1.1%)	2 (1.4%)	1 (0.8%)	
Tx	1 (0.4%)	0	1 (0.8%)	
Liver background				0.031
Cirrhosis	253 (94.4%)	126 (91.3%)	127 (97.7%)	
Hepatitis	15 (5.6%)	12 (8.7%)	3 (2.3%)	

Predictive factors for post-hepatectomy liver failure

Predictive factors for PHLF are shown in Table 5. In univariate analysis, several factors were significantly correlated with PHLF including preoperative serum albumin, bilirubin, aspartate aminotransferase, international normalized ratio (INR), alpha-fetoprotein, MELD score, portal vein invasion, LR extent, Pringle's maneuver, operation time, blood loss, blood transfusion, tumor size, presence of microvascular invasion, perineural invasion, tumor stage, tumor grade, and pathologically proven LC. In multivariate analysis, preoperative serum albumin, bilirubin, INR, and pathologically proven LC were significant predictors of PHLF.

Discussion

Chronic HCV infection is a major health problem in Egypt. Egypt has one of the highest worldwide prevalence of HCV infection (genotype 4), which is attributed to the mass treatment practice of schistosomiasis by unsafe intravenous injections during the period of the 1950s and the 1960s. As a consequence, the incidence of HCC is steadily rising among Egyptian patients [4, 22].

HCV infection differs from other risk factors for the development of HCC. HCV infection is characterized by slow and long-time progression to develop cirrhosis-related HCC [23]. So, patients with HCV-related HCC are unique owing to the

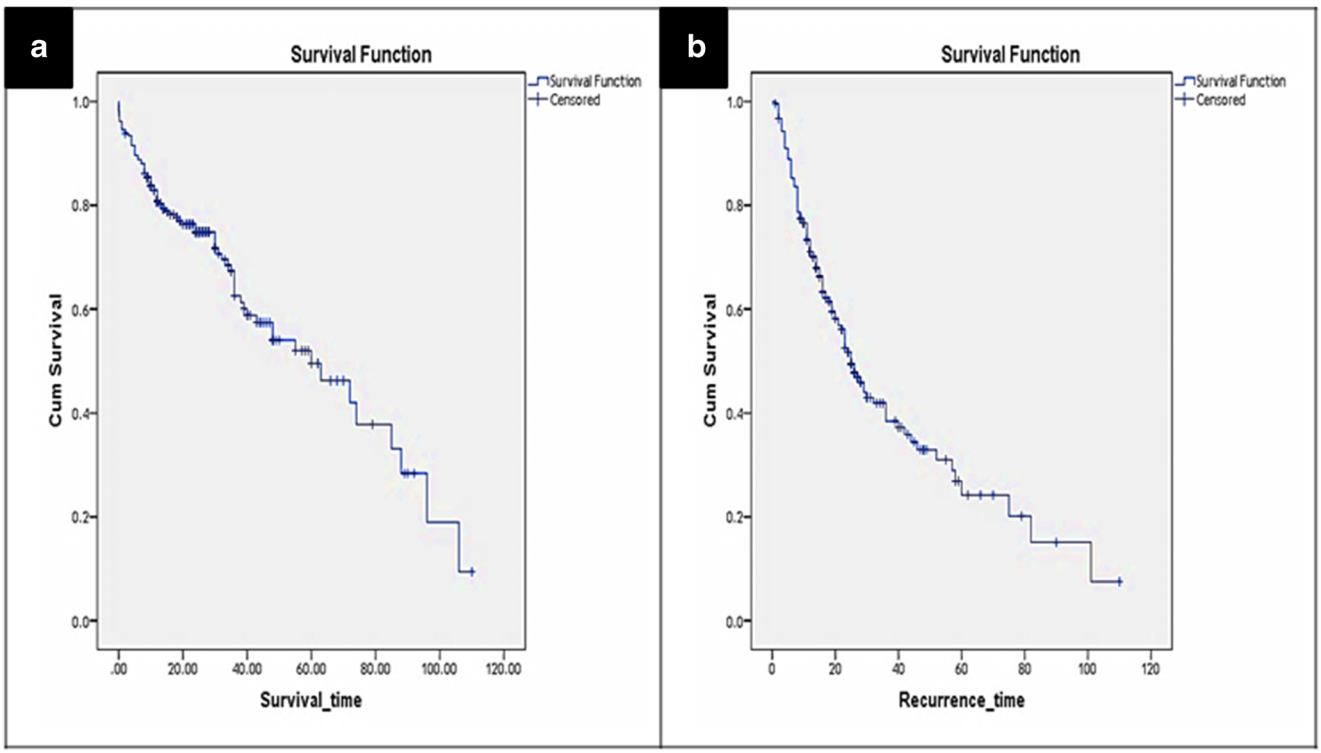

Fig. 2 Kaplan-Meier survival curves of all of the study patients. **a** Overall survival curve. **b** Disease-free survival curve

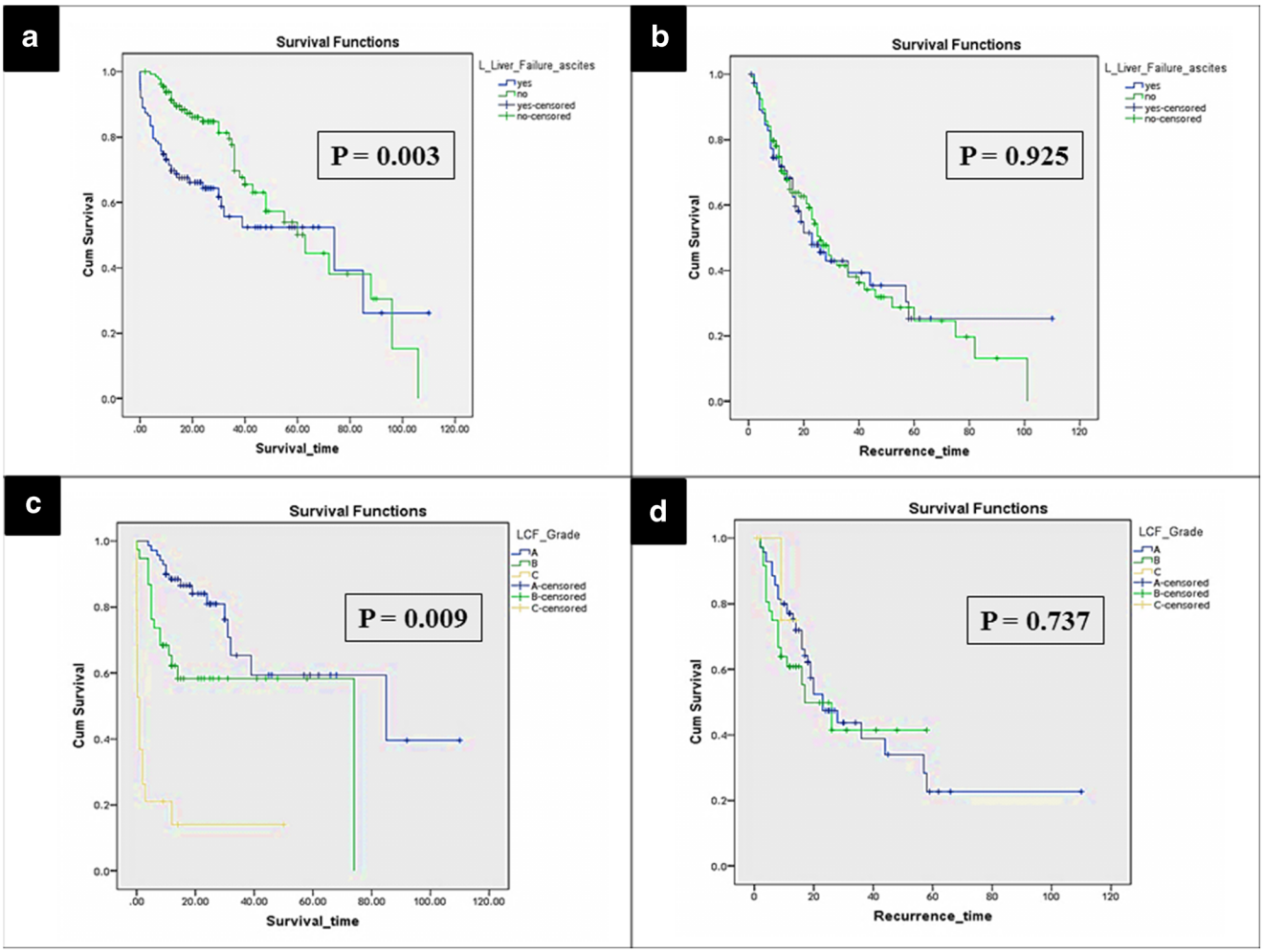

Fig. 3 Comparative Kaplan-Meier survival curves of different groups. **a** Overall survival curve of the two study groups. **b** Disease-free survival curve of the two study groups. **c** Overall survival curve of the different grades of post-hepatectomy liver failure. **d** Disease-free survival curve of the different grades of post-hepatectomy liver failure

background of severe LC. Cirrhotic patients have higher morbidity and mortality rates after LR when they are compared with non-cirrhotic patients [24]. Minor LR in patients with underlying liver cirrhotic is often associated with a high incidence of liver decompensation, refractory ascites, and wound-related complications [25].

PHLF is one of the most feared morbidity after LR for HCC on a background of LC [9]. PHLF and ascites are the primary causes of high early postoperative mortality after LR for HCC [26]. The reported incidence of PHLF after LR for HCC ranged between 1.2 and 38% [10–13, 27–30]. In the current study, the incidence of PHLF was 48.5%, which is high compared with other studies. This can be explained by two reasons. Firstly, 95% of our study patients had underlying pathologically confirmed LC. The main underlying liver disease was HCV infection in 91.8% of all study patients and in 95.4% of patients who experienced PHLF. Secondly, most of the PHLF patients had grade A liver failure only (73 patients—56.2%). Those patients had just biochemical laboratory abnormalities and did not require any additional therapy. The performance and the outcomes of patients with grade A liver failure are very similar to those patients who did not experience PHLF.

The International Study Group of Liver Surgery (ISGLS) proposed a standard definition and a grading system of PHLF [18]. It is simple, easily applicable, and well standardized and allows easy comparison between different centers. In the current study, the ISGLS definition could successfully identify patients with PHLF and detect its association with early postoperative mortality. However, the performance of different grades of PHLF is variable [31]. A future reconsideration of the ISGLS definition may be needed to distinguish patients with just biochemical laboratory abnormalities (grade A PHLF) and patients requiring further management (grade B and C PHLF).

A high recurrence rate after LR adversely affects the prognosis of HCC patients. The presence of coexisting background LC is associated with a higher recurrence rate which could be

Table 4 Recurrence and survival data of the study patients (*TACE*, trans-arterial chemo-embolization; *RFA*, radiofrequency ablation; *MWA*, microwave ablation)

Variables	All cases ($N = 268$)	Non-PHLF group ($N = 138$)	PHLF group ($N = 130$)	p value
Mortality	85 (31.7%)	37 (26.8%)	48 (36.9%)	0.112
Recurrence	125 (46.6%)	72 (52.2%)	53 (40.8%)	0.307
Recurrence time (month)	14 (4–110)	15 (4–101)	12.5 (4–110)	0.061
Recurrence site				0.852
Intrahepatic	96 (35.8%)	54 (39.1%)	42 (32.3%)	
Extrahepatic	5 (1.9%)	3 (2.2%)	2 (1.5%)	
Both	24 (9%)	15 (10.9%)	9 (6.9%)	
Intrahepatic site				0.086
Liver margin	2 (0.7%)	2 (1.4%)	0	
Same liver lobe	27 (10.1%)	18 (13%)	9 (6.9%)	
Other liver lobe	38 (14.2%)	16 (11.6%)	22 (16.9%)	
Bilobar	53 (19.8%)	33 (23.9%)	20 (15.4%)	
Intrahepatic treatment				0.643
Resection	2 (0.7%)	2 (1.4%)	0	
TACE	35 (13.1%)	22 (15.9%)	13 (10%)	
RFA	9 (3.4%)	4 (2.9%)	5 (3.8%)	
MWA	5 (1.9%)	2 (1.4%)	3 (2.3%)	
Combined therapy	12 (4.5%)	7 (4.9%)	5 (3.8%)	
Supportive	57 (21.3%)	32 (23.1%)	25 (19.2%)	
Extrahepatic site				0.688
Lung	10 (3.7%)	5 (3.6%)	5 (3.8%)	
Bone	5 (1.9%)	4 (2.9%)	1 (0.8%)	
Brain	1 (0.4%)	1 (0.7%)	0	
Peritoneum	5 (1.9%)	3 (2.2%)	2 (1.5%)	
Adrenal gland	1 (0.4%)	0	1 (0.8%)	
Abdominal wall	1 (0.4%)	1 (0.7%)	0	
Lymph nodes	1 (0.4%)	1 (0.7%)	0	
Multi-site	5 (1.9%)	3 (2.2%)	2 (1.5%)	

explained by multicentric carcinogenesis [32]. Previous studies had reported several risk factors that affect the recurrence and the prognosis of HCC patients. These risk factors can be classified into tumor-related, procedure-related, and patient-related factors [33–36]. Lurje et al. in a study evaluating recurrence and survival after curative intent partial LR for HCC addressed that tumors within Milan criteria, macrovascular invasion, and tumor stage were independently associated with recurrence, while macrovascular invasion and MELD score were independently associated with survival [37]. Iguchi et al. in a study investigating the relationship of PHLF and HCC recurrence demonstrated the harmful effects of postoperative liver damage on HCC recurrence. However, the underlying mechanism remains unclear. They postulated that postoperative liver damage may provide an environment that allows circulating tumor cells to colonize the liver through disruption of sinusoidal endothelial cells [38]. Similarly, Fukushima et al. addressed the correlation between PHLF and HCC recurrence [10]. They explained this to the upregulation of cytokines including hepatocyte growth factor after liver injury. These cytokines play a key role in the process of liver regeneration and are involved in the growth and progression of HCC [39, 40]. In our study, we did not find any significant differences between patients who experienced PHLF or not in terms of HCC recurrence and DFS rates. Similarly, there were no significant differences between the different grades of PHLF regarding HCC recurrence and DFS rates.

On the other hand, a significantly worse OS was observed in patients with PHLF in our study. Also, patients with grades B and C PHLF experienced worse OS compared with grade A patients. The similar finding had been reported by previous studies [10, 38]. As a possible explanation, Fukushima et al. speculated that patients with PHLF had a less functional liver parenchymal reserve compared with others. This limited their chances of receiving more aggressive treatment lines when they experienced HCC recurrence [10].

Table 5 Predictive factors of post-hepatectomy liver failure (*TACE*, trans-arterial chemo-embolization; *RFA*, radiofrequency ablation; *MELD*, model for end-stage liver disease)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.062 (0.122–0.239)	0.625		
Gender	0.928 (0.305–0.06)	0.806		
Albumin	1.082 (0.281–0.861)	0.001	2.102 (0.302–0.743)	0.014
Bilirubin	1.304 (0.367–0.615)	0.001	0.399 (0.295–0.920)	0.02
Alanine aminotransferase	0.007 (0.004–2.976)	0.085		
Aspartate aminotransferase	0.008 (0.003–0.442)	0.011	0.997 (0.003–1.542)	0.461
International normalized ratio	3.837 (1.148–11.17)	0.001	0.102 (1.234–3.410)	0.04
Platelets	0.003 (0.002–2.761)	0.097		
Creatinine	0.211 (0.532–0.157)	0.692		
Alpha-fetoprotein	0.00 (0. 12–0.451)	0.042	1.745 (0.557–2.016)	0.782
Child-Pugh grade	1.001 (0.846–1.4)	0.237		
MELD score	0.303 (0.083–13.37)	0.001	0.96 (0.041–1.121)	0.735
Hepatitis C virus	0.997 (0.495–4.051)	0.872		
Hepatitis B virus	0.64 (1.231–0.271)	0.603		
Tumor site	0.101 (0.167–0.365)	0.546		
Portal vein invasion	1.303 (0.429–9.233)	0.002	1.761 (0.497–1.298)	0.255
Liver resection extent	1.086 (0.316–11.798)	0.001	0.868 (0.458–0.096)	0.757
Pringle procedure	0.924 (0.363–6.491)	0.011	2.373 (0.423–4.171)	0.069
Operation time	0.6 (0.125–23.103)	0.001	0.713 (0.188–3.243)	0.072
Blood loss	0.001 (0–19.752)	0.001	1 (0.000–2.304)	0.129
Blood transfusion	1.006 (0.252–15.901)	0.001	1.125 (0.349–0.114)	0.735
Morbidity	2.431 (36.09–0.435)	0.995		
Tumor size	0.129 (0.039–10.846)	0.001	0.959 (0.05–1.704)	0.401
Number (Single/multiple)	0.059 (0.359–0.027)	0.868		
Resection margin (R0/R1)	0.152 (0.384–0.157)	0.692		
Capsular invasion	0.289 (0.254–1.295)	0.255		
Microvascular invasion	0.782 (0.249–9.822)	0.002	0.599 (0.640–0.641)	0.423
Perineural invasion	0.857 (0.255–11.311)	0.001	3.353 (0.65–3.369)	0.063
Tumor grade	0.579 (0.179–10.476)	0.001	0.668 (0.208–3.761)	0.052
Tumor stage	0.441 (0.188–5.466)	0.019	1.069 (0.2360–0.08)	0.778
Liver background (cirrhosis/hepatitis)	1.394 (0.658–4.495)	0.034	0.19 (0.236–0.760)	0.029

We analyzed the predictive factors for the development of PHLF. We found that preoperative serum albumin, bilirubin, INR, and pathologically proven LC were the significant predictors of PHLF. Preoperative serum albumin, bilirubin, and INR are well-known predictive factors of liver function reserve and survival outcomes after LR [41, 42]. Previous studies had shown that the presence of impaired preoperative liver functions and the underlying liver parenchymal disease were significant predictors of impaired postoperative liver function [25, 28, 34, 43]. Other studies had identified other operative factors as the extent of hepatectomy, intraoperative blood loss, and transfusion requirement to be associated with the development of PHLF after LR for HCC [10, 38]. On the contrary, we did not find any significant association between different operative parameters and the development of PHLF in our study patients. The application of other modalities for preoperative evaluation of liver status as indocyanine green retention and liver stiffness measurement may help to appropriately select the appropriate extent of LR.

Our study had some limitation including a single-center retrospective study which is liable to some selection bias. Both groups were not matched in the baseline and tumor characteristics. Also, some perioperative variables may not be included in our analysis. A future multicenter study among Egyptian centers including a larger number of HCC patients is needed to confirm our findings.

Conclusions

In conclusion, Egyptian patients with HCC experienced a higher incidence of PHLF after LR for HCC, defined, and graded according to ISGLS definition. The presence of impaired preoperative liver functions and LC was the predictive factors for PHLF. The long-term survival of HCC patients is significantly reduced with the development of PHLF after LR. Prevention of the development of PHLF after LR for HCC can improve the long-term survival of HCC patients by proper selection based on preoperative liver functions and liver parenchymal status.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Informed consent Informed consent prior to the surgical procedure was obtained from all patients.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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