Prediction of Liver Failure after Resection of Hepatocellular Carcinoma in Cirrhotic Patients Efficiency of Different Prognostic Scores

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ABSTRACT

Background: *Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. Liver failure is a fatal complication that sometimes follows a partial hepatic resection. The incidence of post-resectional liver failure (PLF) is most common complication after hepatic resection.* ***Objective:*** *To predict liver failure after hepatic resection of hepatocellular carcinoma in cirrhotic patients by using different scores. [Child-Pugh, MELD scores].* ***Patients and methods:*** *prospective hospital based study General Surgery department and Al-Rajhi University Hospital, in period between June 2011 and June 2016, seventy patients were enrolled in the study.* ***Results****: this study showed that low serum albumin, Child score (> 6) and MELD score (> 9) were independent risk factors for PHLF however considering child pugh score alone or MELD score alone may not be good predictive factor to determine the outcome after resection* ***Conclusion:*** *the consideration of both MELD and child score in the same time for every patient is essential to determine the outcome of surgery after resection for HCC on top of cirrhosis.*

Keywords: *Post- hepatoectomy liver failure, Liver cirrhosis, prognostic scores.*

INTRODUCTION

Liver failure is a fatal complication that sometimes follows a partial hepatic resection. In general, post-resectional liver failure (PLF) is characterized as failure of one or more of the hepatic synthetic and excretory functions that include hyperbilirubinaemia, hypoalbuminaemia, prolonged prothrombin time, elevated serum lactate and/or different grades of hepatic encephalopathy [1].

According to 50–50 criteria; PLF is described as prothrombin index <50% (INR >1.7) and serum bilirubin >50μmol/L (2.9mg/dL) on post-operative day 5. Also, a peak bilirubin of 7.0 mg/dL (120 μmol/L) was identified as a sensitive and specific for prediction of PLF related death [2].

The incidence of post-resectional liver failure (PLF) varies between 0.7 and 9.1%. In the past decade, mortality after partial hepatic resection ranged from 0 to 5% and although the cause of death after partial hepatic resection is multifactorial, PLF seems to be the main cause (18–75%) [3].

The number of hepatic segments resected significantly correlated with the post-operative complication rate. Remnant liver volume (RLV) that is defined as percentage remaining functional volume compared with the exact amount of residual liver mass required to preserve sufficient liver function is unknown. But in general this is mainly depended up on the pre-operative hepatic status before where RLV ≥25–30% in otherwise healthy livers and RLV should be as high as 40% consistent with a good post-sectional outcome[4].

PATIENTS AND METHODS

Type of the study: Prospective hospital based study.

Site and time: General Surgery department and Al-Rajhi University Hospital, in period between June 2011 and June 2016. Seventy patients were enrolled in the study.

Inclusion criteria: All patients had undergone hepatic resection secondary to HCC on top of liver cirrhosis in the above mentioned period will be included.

Exclusion criteria:

- Patients who are on anticoagulants therapy
- Patients who are on regular dialysis
- Patients were unfit for surgery

Pre-operative assessment:

All the patients underwent clinical evaluation, laboratory investigations, and imaging studies. then base line MELD and Child –Pugh score estimated

Operative technique

- **Anesthesia**

The operation was performed under general anesthesia involving tracheal intubation and controlled ventilation. Isoflurane in an air-oxygen mixture, was the most commonly used anaesthetic agent, supplemented with intravenous narcotic.

Laparoscopic assessment was performed if the radiological assessments were inconclusive.

1- Post-operative care

Full blood count, renal and liver function and coagulation profile were checked daily. Oral fluids were started on 30 ml/hr from the first postoperative day, and were increased as tolerated. Drain was removed if output is less than 50 ml/day.

Follow up

All patients were followed up at the outpatient clinic weekly for the first month and weekly for 3 months. At each follow-up, clinical, biochemical, and US assessments of patients were carried out. The level of the tumor marker, α-fetoprotein, was also measured. On suspicion of recurrence, an abdominal MSCT scan was performed

Outcome measurement

The primary outcome was development of liver cell failure after resection based on the International Study Group of Liver Surgery (ISGLS) proposed a standardized definition and severity of grading of PHLF; PHLF was defined as "a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5.

Secondary outcomes:

- Morbidity with special emphasis on bleeding and biliary complications, infective complications, re-laparotomies and re-admissions.
- Hospital stay and ICU stay.
- 3-month mortality.

Statistical analysis

- All calculations were performed with the SPSS 16.0 statistical package (SPSS, Inc., Chicago, IL)
- Probability (p) < 0.05 was considered statistically significant

Ethical consideration

Approval of the study from the local ethics committee had been obtained

RESULTS

The current study was performed in period between June 2011 and June 2016 at department of General Surgery and Al-Rajhi University Hospital, Assiut University Hospitals, Faculty of Medicine, Assiut University. Seventy patients were enrolled in the study.

Demographic and Clinical data of the studied patients:

Table (1) showed that demographic and clinical data of studied patients.

Table 1: Demographic and Clinical data of the studied patients

Variables	n= 70
Age (years)	
Mean ± SD	56.98 ± 3.6
Range	39- 64
Sex	
Male	49 (70%)
Female	21 (30%)
Underlying liver disease	
Hepatitis C infection	63 (90%)
Hepatitis B infection	4 (5.7%)
Non-B non- C hepatitis	3 (4.3%)
Comorbidities	
Nothing	39 (57.7%)
Diabetes mellitus	15 (21.4%)
Hypertension	10 (14.3%)
Cardiac disease	6 (8.6%)
Clinical presentation at time of diagnosis	
Accidently discovered	45 (64.3%)
Abdominal pain	15 (21.4%)
Jaundice	5 (7.1%)
Abdominal mass	3 (4.3%)
Weight loss	2 (2.9%)

Baseline Laboratory Data of the studied patients:

Table (2) showed mean (± SD) of baseline laboratory data of the studied patients. All baseline laboratory data were within normal range with exception of mild raised liver enzymes. Also, there was marked elevation in level of alpha feto protein; 265.44 ± 90.9 ng/ml.

Majority of patients were Child A while 16 (23%) patients were Child B. mean of MELD score was 9 ± 2.

Table 2: Baseline Laboratory data of the studied patients

Variables	Mean ± SD
Complete Blood Picture	
Hemoglobin (g %)	11.34 ± 1.3
Platelets (x 10^3/l)	145.89 ± 54
White blood cells (x 10^3/l)	3.5 ± 1.09
PT (seconds)	13 ± 3
PC (%)	79 ± 8
INR	1.2 ± 0.2
Liver function tests	
Total bilirubin (mg %)	1.01 ± 0.05
ALT(U/l)	87 ± 15
AST (U/l)	111 ± 10
Albumin (g/l)	36.23 ± 3.6
Total protein (g/l)	70.8 ± 3.12
Kidney function tests	
Creatinine (mg\dl)	1.02 ± 0.42
Urea (mg/dl)	4 ± 3
Serum electrolytes	
Sodium (µmol/l)	132.09 ± 3.98
Potassium (µmol/l)	4.02 ± 1.09
Alpha fetoprotein (ng/ml)	265.44 ± 90.9
MELD score	9 ± 2
Child classification	
A	54 (77%)
B	16 (23%)

Frequency of liver cell failure and other complications in the current study:

The main outcome measures were perioperative mortality and morbidity. Morbidity was defined as the development of one or more postoperative complications.

Table 3: Post-operative Complications

Post-operative complications	Frequency (Percentage of total complications)
PHLF	23 (85.1%)
Bile leak	2 (2.8%)
Wound infection	7 (10%)
Internal hemorrhage	2 (2.8%)
Abdominal collection	1 (1.4%)
Pleural effusion	1(1.4%)

Patients of the current study were further divided into two groups; the first group who developed PHLF (n= 23) and the second group who didn't (n= 47) and we studied the possible predictors for decompensation.

Comparison between the demographic and clinical data of both groups:

Table 4: Demographic and Clinical data of both groups

Variables	PHLF (n= 23)	No PHLF (n= 47)	*P* value
Age (years)			0.99
Mean ± SD	57.98 ± 3.7	55.32 ± 3.1	
Sex			
Male	14 (61%)	41 (87%)	0.45
Female	4 (39%)	11 (13%)	
Underlying liver disease			
Hepatitis C infection	21 (91%)	42 (89.3%)	0.06
Hepatitis B infection	1 (4.5%)	3 (6.4%)	
Non- B non C hepatitis	1 (4.5%)	2 (4.3%)	
Comorbidities			
Nothing	10 (43.5%)	29 (61.7%)	
Diabetes mellitus	4 (17.4%)	11 (23.4%)	0.11
Hypertension	8 (34.7%)	2 (4.2%)	
Cardiac disease	1 (4.4%)	5 (10.7%)	
Clinical presentation			
Accidently discovered	14 (60.8%)	32 (68%)	
Abdominal pain	4 (17.4%)	11 (23.4%)	0.34
Jaundice	2 (8.8%)	2 (4.3%)	
Abdominal mass	3 (13%)	0	
Weight loss	0	2 (4.3%)	

Baseline laboratory data of both groups

Table 5: Baseline Laboratory data of both groups

Variables	PHLF (n= 23)	No PHLF (n= 47)	*P* value
Complete Blood Picture			
Hemoglobin (g %)	11.45 ± 0.95	12.04 ± 1.23	0.76
Platelets (x 10^3/l)	135.11 ± 17	150.09 ± 22	0.65
White blood cells (x 10^3/l)	3.15 ± 0.23	45 ± 1.1	0.11
PT (seconds)	14 ± 2	11 ± 3	**0.03**
PC (%)	75 ± 7	81 ± 6	**0.01**
INR	1.2 ± 0.22	1.1 ± 0.27	**0.02**
Liver function tests			
Total bilirubin (mg %)	1.12 ± 0.21	0.99 ± 0.05	**0.04**
ALT(U/l)	89 ± 11	80 ± 10	0.34
AST (U/l)	123 ± 5	101 ± 22	0.22
Albumin (g/l)	32.11 ± 0.29	37.39 ± 3.3	**0.00**
Total protein (g/l)	78.8 ± 0.12	90.8 ± 0.21	0.08
Kidney function tests			
Creatinine (mg\dl)	1.01 ± 0.34	0.95 ± 0.52	0.79
Urea (mg/dl)	4 ± 3	3.31 ± 1.23	0.21
Serum electrolytes			
Sodium (µmol/l)	131.23 ± 21.93	134.09 ± 20.18	0.74
Potassium (µmol/l)	4.22 ± 0.32	3.99 ± 1.32	0.21
Alpha fetoprotein (ng/ml)	267.01 ± 88.07	263.99 ± 90.11	0.38
MELD score	10 ± 2	8 ± 2	**0.01**
Child score			**0.02**
A	13 (56.5%)	41 (87.2%)	
B	10 (43.5%)	6(12.8%)	

Outcome, morbidity and hospital stay in both groups

Table 6: Outcome, morbidity and hospital stay in both groups

Variables	PHLF (n= 23)	No PHLF (n= 47)	*P* value
Other Post-operative complications	10 (43.5%)	3 (5.8%)	**0.00**
Hospital stay (days)	14.56 ± 3.67 5- 34	8.06 ± 3.05 7- 15	**0.01**
Outcome			
Alive	18 (78.2%)	47 (100%)	**0.03**
Dead	5 (21.8%)	0	

Multivariate Regression analysis for Prediction of PHLF

The current study showed that low serum albumin, Child score (> 6) and MELD score (> 9) were independent risk factors for PHLF ((OR= 2.11, 95% CI= 2.11- 3.89, *P*= 0.01), (OR= 2.88, 95% CI= 0.34- 0.99, *P*= 0.02) and (OR= 1.7, 95% CI= 1.55- 4.99, *P*= 0.01)) respectively.

Table 7: Multivariate Regression analysis for prediction of PHLF

Variables	OR	95% CI	*P* value
Impaired coagulation profile	1.2	1.2- 3.22	0.08
Raised bilirubin	2.1	0.93- 1.89	0.33
Low serum albumin	2.11	2.11- 3.89	**0.01**
Child score (> 6)	2.88	0.34- 0.99	**0.02**
MELD score (> 9)	1.7	1.55- 4.99	**0.01**
Major resection	1.02	0.76- 0.99	0.35

DISCUSSION

Hepatocellular carcinoma (HCC) is a primary malignancy of hepatocellular origin .It is the fifth most common tumor worldwide, and it is currently the third leading cause of cancer-related death and accounts for more than 90% of all primary liver cancer. In the past, Egypt was similar to the western countries with an overall frequency of 2.3% among other types of cancer. However, currently, HCC appears to have been increasing over the last decade **[5].**

In Egypt, over a decade, there was nearly a two-fold increase in the proportion of HCC among chronic liver disease (CLD) patients, with a significant decrease in hepatitis B virus and a slight increase in hepatitis C virus (HCV) as risk factors. Increased detection of small lesions at presentation reflects increased awareness of the condition **[6].**

The current study included 70 patients underwent for HCC on top of Cirrhosis with mean age was 56.98 ± 3.6 years with range between 39-64 years. Males' sex represented 49 (70%) patients in the study while females were 21 (30%).

Collectively of 70 pt. 23pt (32.8%) developed PHLF based on criteria of the International Study Group of Liver Surgery (ISGLS) proposed a standardized definition and severity of grading of PHLF; PHLF was defined as "a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5.

A study was done by **Cucchett et al.** , included 154 patients, 11 (7.1%) patients had developed PHLF while 143 didn't develop. The median age was 64 years (range, 41-81) **[7]**. Another study was performed by **Taha et al.** , included 208 patients where there were 157 male (75.5%) and 51 female (24.5%) patients, with a mean age of 55.4 ± 9.3 years (range from 26 to 75 years), a total 20 (9.6%) patients developed PHLF**[8]**. Other study by **Xiao et al .** showed that 10.1% patient from 167 patients included in the study developed PHLF**[9]**.

The big difference in the percentage of the patients developed PHLF in our study and those in the previous studies may be suggested due to the grade difference of the patient selected for resection in our patient and the patients of others or it may be due to the type and extent of resection done in each study.

In study of **Taha et al.** the most common symptom was right hypochondrial dull aching pain in 152 (73.1%) patients and was accidentally discovered in 31 patients (14.9%); jaundice was found in four patients (1.9%) due to infiltration of the biliary system. weight loss, and internal hemorrhage, which account for 1% each. A total of 165 patients (79.3%) were positive for HCV markers, five patients (2.2%) were positive for hepatitis B virus surface antigens (HBsAg), whereas seven patients (3.4%) were positive for both virus markers. Most of the patients were in Child–Pugh class A [183 (88%)], and the other 25 (12%) patients were in Child–Pugh class B. and these data are in accordance with our current study which should respectively**[8]**.

In the current study majority of the patients 45 (64.3%) were accidently discovered while only 5 (7.1%), 3 (4.3%) and 2 (2.9%) patients presented with jaundice, abdominal mass and weight loss. Abdominal pain was the main feature in 15(21.4%) patients. Majority of patients were Child A while 16 (13%) patients were Child B. mean of MELD score was 9 ± 2.

Taha et al. , mentioned that the most frequent etiology of liver cirrhosis HCV infection and this is in agreement of the data of our current study while they are in disagreement with it published by **Xiao et al.,** who reported that the most

etiology of the studied patients were HBV and this is again going with our study[8], [9].

Major resection was done in 18 (25%) patients while minor and localized resections were done in 40 (57%) and 12 (17%) patients respectively. Sixty five (92.9%) patients were transfused during operation and Pringle's maneuver was done in 25 (35.7%) patients. Range of operative time ranged between 3 and 6 hours with mean (±SD) was 3.01 ± 0.96 hours.

Wound infection occurred in 7(10%) while Internal hemorrhage was observed in 2 (2.8%) patients, Bile leak occurred in 2 (2.8%) patients also.Both Abdominal collection and Pleural effusion presented in 1(1.4%) patients collectively the postoperative complications were 18.5% and this is nearly going with results reported by **Xiao et al.** who showed that the frequency of post-operative complication occurred in 31.3% and the pleural effusion and intrabdominal abscess were the frequent complications in addition to the PHLF[10]. And in the same time these data are in concordance with those reported by **Cucchett et al [7].**

Its worthy to mention that serum bilirubin and portal hypertension are independent prognostic factors for overall survival after resection **Bruix et al.[10]**.

It is thought that both the surgical curability and the post-operative hepatic functional preservation are crucial for the successful treatment of patients with HCCs. Especially in patients with cirrhosis, smaller surgical margins would prevent post-operative complications better, including liver failure, although there is a concern of recurrence in the remnant liver. For patients with cirrhosis, the balance between the surgical curability and the preservation of function of the remnant liver is of considerable importance **Imamura et al., [11].**

Cucchett et al. demonstrated that MELD score can accurately predict both postoperative liver failure and postoperative morbidity of cirrhotic patients undergoing resection for HCC. A MELD score equal to or above 11 prior to surgery lead to a very high incidence of liver failure (37.5%) and postoperative complications (83.3%), resulting in a significantly longer hospital stay and a lower 1-year survival in comparison to patients with lower MELD scores, and actually this is in agreement with our study to some extent [7].

It is worthy to mention that our study declared very important issue that, considering child pugh score alone or MELD score alone may not be good predictive factor to determine the outcome after resection, since for some patients with low MELD score but with high child score developed PHLF and vice versa patient with high MELD score and low child score again developed PHLF.

Both scores were in reasonable rang and so considering both scores in the same patient is preferable in determination the outcome after resection.

CONCLUSION & RECOMMENDATIONS

The study showed that low serum albumin, Child score (>6) and MELD score (>9) were independent risk factors for PHLF. These findings underscore the need for effective selection for high risk patients to prevent an adverse outcome after resection.

So, these three factors can accurately predict liver cell failure and morbidity in patients with HCC on top of cirrhosis undergoing hepatic resection. Cirrhotic patients with a low serum albumin, Child score (>6) and/ or MELD score (>9) are at high risk of postoperative liver cell failure and complications and should be referred for other treatments. Cirrhotic patients with high serum albumin, Child score (< 6) and MELD score (<9) treated with minor hepatic resectionsachieve no mortality and low morbidity rates. Application of these factors in the preoperative assessmentof liver function prior to hepatic resection is recommended.

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Both scores were in reasonable rang and so considering both scores in the same patient is preferable in determination the outcome after resection.

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