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Fibroscan and FIB-4 Assessment Versus Lymphocyte / Monocyte Ratio as Predictors of Post-Hepatectomy Liver Failure in HCV Egyptian Patients with Hepatocellular Carcinoma

Mona Nasef[1, *], Lobna Abo Ali[1], Mohammed Hablus[2], Hossam Eldeen Soliman[3], Nehad Hawash[1], Nadia Elwan[1]

[1]Tropical Medicine and Infectious Diseases Department, Faculty of Medicine, Tanta University, Tanta, Egypt

[2]Gastrointestinal, Liver and Laparoscopic Surgery Department, Faculty of Medicine, Tanta University, Tanta, Egypt

[3]HPB and Liver transplantation surgery Department, National Liver Institute, Menoufia University, Menoufia, Egypt

Email address:
mona.nasef@med.tanta.edu.eg (M. Nasef), Mohamed.habls@med.tanta.edu.eg (M. Hablus), lobna.aboali@med.tanta.edu.eg (H. E. Soliman),
Hosam123mail@yahoo.com (H. E. Soliman), nehad.hawash@med.tanta.edu.eg (N. Hawash), nad.dec1983@gmail.com (N. Elwan)
*Corresponding author

Abstract: Background: Post-hepatectomy liver failure (PHLF) is the most leading cause of mortality in patients diagnosed with hepatocellular carcinoma (HCC) and undergoing resection of the affected part of the liver. Objectives: This research aimed to determine the value of the lymphocyte to monocyte ratio (LMR), fibrosis score 4 (FIB-4) and liver stiffness measurements (LSM) using Fibroscan as pre-operative predictors of PHLF in Egyptian patients with post- hepatitis C virus (HCV) liver cirrhosis and HCC. Methods: In this prospective cohort study definition of PHLF was done according to the "50-50 criteria". Multivariate analysis was done to identify PHLF independent predictors. The predictive accuracy of the pre-operative LMR, FIB-4 and LSM with Fibroscan were evaluated by receiver operating characteristic (ROC) curve. Results: Enrollment of fifty Egyptian patients was done. 14 patients (28%) experienced PHLF. The presence of oesophageal varices, serum AST, serum albumin, LMR, FIB-4 score, and LSM (P<0.05) were independent pre-operative predictors for PHLF. According to ROC curve analysis, LMR yielded the best accuracy for predicting PHLF at cutoff <3.33 [AUC = 0.940; sensitivity = 93.65%; specificity = 94.44%; positive predictive value = 86.67%; negative predictive value = 97.14%]. FIB-4 score and LSM had lower AUC (0.886 and 0.875) respectively. Conclusion: The pre-operative LMR has a higher predictive ability for PHLF in patients with HCV-related HCC undergoing hepatectomy compared with FIB-4 score and LSM using Fibroscan.

Keywords: Hepatocellular Carcinoma, Resection, Post-hepatectomy Liver Failure, Lymphocyte to Monocyte Ratio, Fibroscan, Fibrosis Score 4

1. Introduction

An epidemiological study from Egypt had revealed that liver cancer forms; 1.68% of the total malignancies, 11.75% of the malignancies of all digestive organs and 70.48% of all liver tumors. Hepatocellular carcinoma (HCC) is considered as a primary cancer of the liver arising from hepatocytes and accounting for 85 to 90% of the entire primary liver cancers [1].

One of the potential curative therapies for HCC is liver resection. But its feasibility is limited in the majority of those patients as most of them have associated chronic liver diseases increasing the risk of post-operative morbidity and mortality [2].

Post-hepatectomy liver failure (PHLF) had been identified as a severe post-operative complication and is considered as the main cause of death following resection of the liver. That is strongly related to cirrhosis, limited residual liver tissue and relatively poor liver regeneration ability. Even with major advances in technology and increasing experience in centers specialized for liver resection; PHLF is still a major problem due to associated high rates of post-operative morbidity (4.09% - 47.7%) and mortality (0.24% - 9.7%) [3].

Various laboratory, imaging techniques and indices have been proposed for proper pre-operative assessment of hepatic functional reserve including serum hyaluronic acid assay, volumetric assessment of the remnant liver, indocyanine green clearance test which is the most commonly used method for quantitative liver function reserve assessment in Asian countries. However, it is expensive and time consuming [4], also Child–Pugh score (CTP) which is the most widely used method for assessment of hepatic function, selecting patients for hepatectomy, and predicting postoperative mortality. However, some limitations of the CTP score in predicting the PHLF have been described [5].

Several studies concluded a significant association between chronic inflammatory diseases and increased incidence of malignancy including HCC [6]. The lymphocyte-monocyte ratio (LMR) is considered as a systemic inflammation-related marker and has recently been investigated in patients with solid tumors as a prognostic marker [7], including patients who had liver resection as a treatment for HCC [8].

It has been shown that the fibrosis score 4 (FIB-4) is effective in the assessment of liver fibrosis and cirrhosis [9, 10], in addition it is known as a good predictor of complications occurring after hepatectomy. However, the accuracy of FIB-4 to predict the short-term results of liver resection in patients with HCC had been investigated by few studies [11].

One of the non-invasive techniques for assessing liver stiffness is transient elastography (Fibroscan) [12]. By differentiating between the degree of liver fibrosis and cirrhosis that subsequently reflect the functional reserve of the liver which is important for patients with HCC undergoing liver resection [13].

However, until now no consensus was reached on the superiority of one of these methods to predict post-operative hepatic dysfunction after hepatic resection. To our knowledge, this is the first study on the predictive ability of LMR for PHLF.

This study aimed to determine the value of the LMR, FIB-4 score and LSM using Fibroscan as pre-operative predictors of PHLF in Egyptian patients with post viral hepatitis C liver cirrhosis and HCC who underwent hepatectomy.

2. Materials and Methods

2.1. Study Design and Patients Selection

This was a prospective cohort study conducted in Egypt.

One hundred and seventeen (117) patients suffering from liver cirrhosis and HCC were screened for participation in this study during the period from September 2017 to September 2019. Of these, 50 patients with liver cirrhosis and HCC after HCV infection who underwent hepatectomy were enrolled. Patients were recruited from the multidisciplinary HCC clinic of Tropical Medicine and Infectious diseases Department in Tanta University Hospital and from the National Liver Institute, Menoufiya University, Egypt.

Before the beginning of this study an approval from faculty of medicine, Tanta University ethical committee was obtained (coded approval number: 31644/07/17) complying with the declaration of Helsinki (1975), in addition an informed written approval was signed by every patient before being enrolled in the study and a code number for each patient was used. All authors had full access to the study data; the final manuscript had been reviewed and accepted by all authors.

Eligibility criteria for treatment of HCC patients by liver resection included: Barcelona Clinic Liver Cancer (BCLC) stages 0-A, adequate liver functional reserve, with Child Turcotte Pugh score (CTP) grade A, good performance status (score of 0–2), infection with HCV and adequate residual liver volume determined by volumetric CT.

Patients received other treatments for HCC before hepatectomy, had vascular invasion, extrahepatic spread, other associated tumors, cardiac, pulmonary, renal or cerebral dysfunction were excluded from this study.

2.2. Diagnosis and Definitions

Liver cirrhosis was diagnosed on the basis of clinical, laboratory findings, imaging, Fibroscan and FIB-4 score. The CTP score was calculated based on its respective formula to assess liver disease severity [14]. HCC grading and resectability were determined by abdominal ultrasonography and contrast-enhanced CT or MRI prior to liver resection. Diagnosis of HCC and cirrhosis were confirmed by post-operative pathological examination. HCC staging using BCLC staging system was done [15].

Clinically significant portal hypertension was established by: Detection of gastro-esophageal varices by upper endoscopy, splenic diameter more than 12 cm and/or count of platelet less than 100×10^9/L [16].

Definition of PHLF was made according to the "50-50 criteria" that is defined as prothrombin time (PT) <50% (international normalized ratio (INR) >1.7) and serum bilirubin >50μmol/L (>2.9 mg/dL) on 5th day post-operative [17].

While post-operatively mortality was defined as death within 30 days following surgery.

2.3. Pre-Operative Assessment

All of the patients in this study were subjected to detailed history, co-morbidities, clinical assessment, laboratory testing including (complete blood picture, liver profile, INR, renal function tests, serum alpha fetoprotein, HBsAg, anti HBc

total, anti-HCV antibody, quantitative PCR for HCV RNA), and radiological data (Ultrasonographic examination of abdomen and contrast-enhanced CT or MRI). While CT volumetry was done to ensure adequate residual liver volume which was 50 percent for patients with cirrhosis. All enrolled patients underwent upper gastrointestinal endoscopy and injection sclerotherapy or band ligation of esophageal varices was done if indicated.

2.4. Calculation of Score Values

Calculation of LMR was done according to equation (1):

Absolute lymphocyte count (/mm^3 or %) / absolute monocyte count (/mm^3 or %) (1) [18].

While the equation (2) used for FIB-4 score was:

Age (years) × (AST [U/L]/platelet count [10^9/L] × ALT [U/L]$^{1/2}$ (2) [19].

2.5. Transient Elastography (Fibroscan)

LSM was done by experienced operators using the Fibroscan (echosens-France) 502 M probe within one week before hepatectomy. Only results with ten valid measurements, a success rate more than 60% and the interquartile range (IQR) less than 30% of the median value were considered valid. Kilopascals (kPa) were the measuring units for these results [20].

2.6. Surgical Technique

Selected patients underwent hepatic resection of HCC focal lesions according to the standard protocols of surgery and anesthesia departments. Laparotomy was done by right subcostal or midline incision. Ultrasonography was used during operation to localize the tumor (s) and to confirm the relationships between the tumor (s) and their surrounding vessels. Either anatomical or non-anatomical resection, was selected on case-by-case basis. During the operation central venous pressure was frequently assessed by the anesthetist. Either Pringle maneuver or selective vascular occlusion of the hemiliver was chosen when needed. Bipolar coagulation, clips, and sutures were used for hemostasis.

2.7. Post-Operative Assessment

Regular follow up of all patients during hospitalization by physical examination and laboratory investigation to detect post-operative complications. Abdominal ultrasound, CT scan and chest X-ray were carried out when indicated. Assessment of PHLF was done on post-operative day 5 and post-operative mortality was reported.

2.8. Statistical Analysis

Statistical program for social science (SPSS) software version 22, 2015 USA was used to analyze data. Mean, standard deviation, median and range were used for description of quantitative variables. While frequency and percentages were used for qualitative variables. In order to compare a quantitative variable between two independent groups in parametric data Unpaired Student t test and Mann-Whitney U test were used. Chi square test was used to compare a qualitative variable between two independent groups. P value was significant if ≤ 0.05. For identification of independent predictors of PHLF multivariable logistic analysis was carried out using a logistic regression model. The area under the receiver operating characteristic (ROC) curve was calculated to measure the discriminatory power of the LMR, FIB-4 score, LSM with Fibroscan (by kpa value) as predictors of PHLF and its 95% confidence interval. To choose the best cut-off we selected the point with both maximum sensitivity and specificity on the ROC curve.

3. Results

One hundred and seventeen (117) patients diagnosed with liver cirrhosis and HCC were screened for enrollment in our study. Out of whom 67 patients were excluded thus, 50 patients with post HCV liver cirrhosis and HCC who underwent hepatectomy were enrolled. All patients in this study tested positive for HCV infection while negative for hepatitis B virus (HBV). PHLF developed in 14 patients (28%) "Figure 1". So, patients were categorized into two groups:

Group I: included 36 patients who did not develop PHLF
Group II: included 14 patients who developed PHLF

The baseline characteristics of patient population according to development of PHLF are summarized in Table 1. In PHLF group, ten patients (71.43%) had oesophageal varices grade 1, nine patients (64.29%) had performance status grade 1, seven patients (50%) had Child score A 6, spleen size and tumor size were significantly increased when compared with patients without PHLF (P≤ 0.05) "Table 1".

Table 1. Baseline characteristics of patient population according to development of PHLF

Parameters		No PHLF (n=36)	PHLF (n=14)	P-value
Age (years); mean±SD		57.06±7.92	59±7.18	0.428
Gender [male, n (%)]		31 (86.11%)	11 (78.57%)	0.514
Co-morbidity, n (%) Diabetes mellitus		11 (30.56)	6 (42.86)	0.410
Hypertension		11 (30.56)	5 (35.71)	0.726
Oesophageal	No n (%)	23 (63.89%)	4 (28.57%)	0.024 *
Varices	Yes (grade 1) n (%)	13 (36.11%)	10 (71.43%)	
Prothrombin concentration (%) mean±SD		85.89 ± 12.18	80.37 ± 14.54	0.281
INR mean±SD		1.13±0.15	1.19±0.14	0.252

Parameters		No PHLF (n=36)	PHLF (n=14)	P-value
Creatinine (mg/dl) mean±SD		0.86±0.18	0.83±0.18	0.691
AFP (ng/ml), median (IQR)		24.5 (6.1-266.25)	42 (4.1-208.75)	0.924
Hemoglobin (g/dl) mean±SD		13.47 ± 1.5	11.63± 1.11	<0.001 *
Platelets (x10³/cmm) mean±SD		162.31 ±61.7	134.57± 47.5	0.137
Total bilirubin (mg/dl) mean±SD		0.81±0.39	1.1±0.21	0.018 *
Albumin (g/dl) mean±SD		4.13±0.48	3.49±0.29	<0.001 *
ALT (U/l) median (IQR)		39.5 (22-65)	50 (28.5-77.75)	0.161
AST (U/l) median (IQR)		41 (27.75-54.25)	73.4 (42.5-87)	0.008 *
Spleen size (cm) mean±SD		13.88±1.57	15.3±0.89	0.003 *
Tumor size (cm) mean±SD		4.97±2.63	7.73±4.24	0.008 *
Performance Status, n (%)	PS0	25 (69.44%)	5 (35.71%)	0.029 *
	PS1	11 (30.56%)	9 (64.29%)	
BCLC stage, n (%)	BCLC 0	6 (16.67%)	0 (0.00%)	0.103
	BCLC A	30 (33.83%)	14 (100%)	
Child score, n (%)	A5	30 (83.33%)	7 (50%)	
	A6	6 (16.67%)	7 (50%)	0.016 *
LM ratio mean±SD		4.62±1.78	2.52±0.52	0.001 *
FIB-4 score mean±SD		3.54±0.65	5.18±1.99	<0.001 *
Fibroscan values (kpa) mean±SD		12.76±3.12	24.34±11.08	0.002 *

Abbreviations: AFP, alpha fetoprotein; ALT, Alanine transaminase; AST, Aspartate transaminase; BCLC, Barcelona clinic liver cancer; FIB-4 score, fibrosis score 4; kpa, kilopascal; INR, international normalizing ratio; IQR, Interquartile range; LM ratio, lymphocyte to monocyte ratio; PHLF, posthepatectomy liver failure; SD, standard deviation; n, number *significant (P ≤ 0.05).

As regards pre-operative laboratory investigations, hemoglobin concentration and serum albumin level showed significant decreases (P<0.001), while total bilirubin and AST were increased significantly in PHLF group when compared with patients without PHLF (P≤ 0.05) "Table 1".

The mean FIB-4 score was increased significantly in PHLF group (5.177±1.988 vs. 3.542±0.654 correspondingly) (P<0.001) and the mean LSM obtained by Fibroscan were significantly higher in PHLF group (24.340±11.076 vs. 12.761±3.122 kpa respectively) (P= 0.002) when compared with those without PHLF "Table 1".

In PHLF group, the mean LMR was significantly decreased compared with patients without PHLF (2.517±0.515 vs. 4.623±1.782 respectively) (P= 0.001) "Table 1".

Regarding post-operative day 5 clinical features and laboratory investigations, patients who developed PHLF had hepatic encephalopathy, jaundice, lower limb edema and ascites which was significantly higher than those with no PHLF (P ≤ 0.05). In patients with PHLF, there were significant increases in INR, total bilirubin, ALT and AST levels (P<0.001) while serum albumin and platelets count significantly decreased in the in PHLF group (P ≤ 0.05) when compared with patients without PHLF "Table 2".

Table 2. *Post-operative day 5 assessment of the studied groups*

Parameters	No PHLF (n=36)	PHLF (n=14)	P-value
INR; mean±SD	1.22 ± 0.17	1.88±0.06	<0.001*
Total bilirubin (mg/dl); mean±SD	1.16±0.51	3.44±0.42	<0.001*
Albumin (g/dl); mean±SD	3.38±0.33	2.74±0.29	<0.001*
ALT (U/l); mean±SD	108.47±41.95	209.79±96.48	<0.001*
AST (U/l); mean±SD	87.56±35.7	178.57±72.3	<0.001*
Platelets (x10³/c.mm); mean±SD	139.36±51.75	98.14±37.48	0.017*
Hepatic encephalopathy, n (%)	0 (0%)	2 (14.29%)	0.021*
Lower limb edema, n (%)	3 (8.33%)	14 (100%)	<0.001*
Ascites, n (%)	1 (2.78%)	13 (92.86%)	<0.001*

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; INR, international normalizing ratio; PHLF, posthepatectomy liver failure; SD, standard deviation; n, number; *significant (P ≤ 0.05).

Post-operative complications occurred in 24 patients (48%) and were more common in patients who developed PHLF when compared with those without PHLF (14 vs. 10 patients) (P=0.001). The most common complication after PHLF was pleural effusion, which occurred in 7 patients (14%) of PHLF group. Two patients died during 30 days of operation as a result of PHLF, with a mortality rate of 4% "Figure 1".
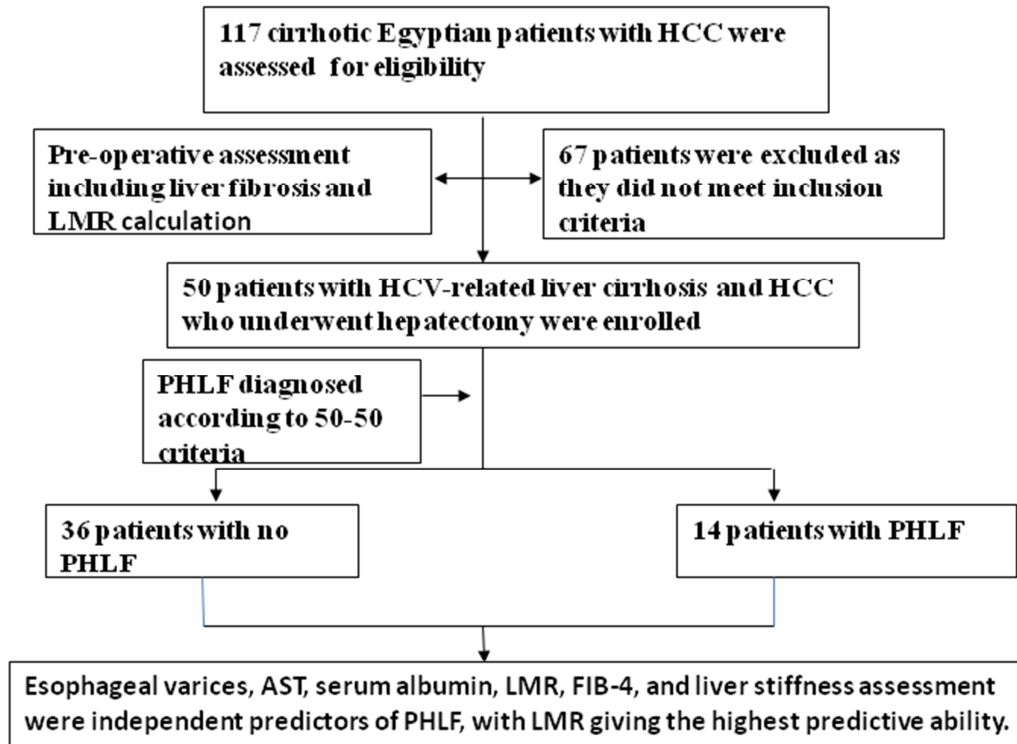
Figure 1. Consort flow diagram showing patients enrollment and follow up

Abbreviations: HCC, hepatocellular carcinoma; LMR, lymphocyte/ monocyte ratio; PHLF, post-hepatectomy liver failure; AST, aspartate aminotransferase; FIB-4, fibrosis score 4.
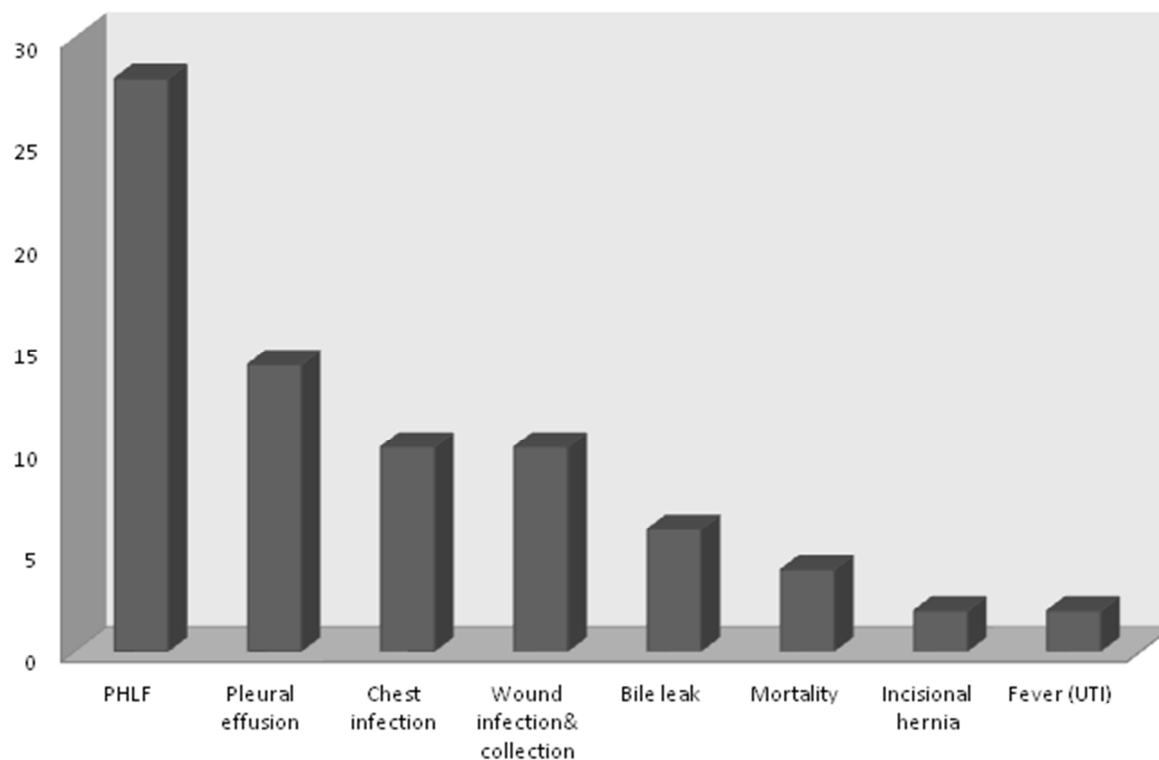
A multivariate logistic regression analysis showed that, presence of oesophageal varices, serum AST, serum albumin, LMR, FIB-4 score, and LSM with Fibroscan (P= 0.040; 0.038; 0.024; 0.001; 0.022, 0.016 respectively) were independent predictors for PHLF "Table 3".

Table 3. Univariate and multivariate analyses for the preoperative predictors of post-hepatectomy liver failure

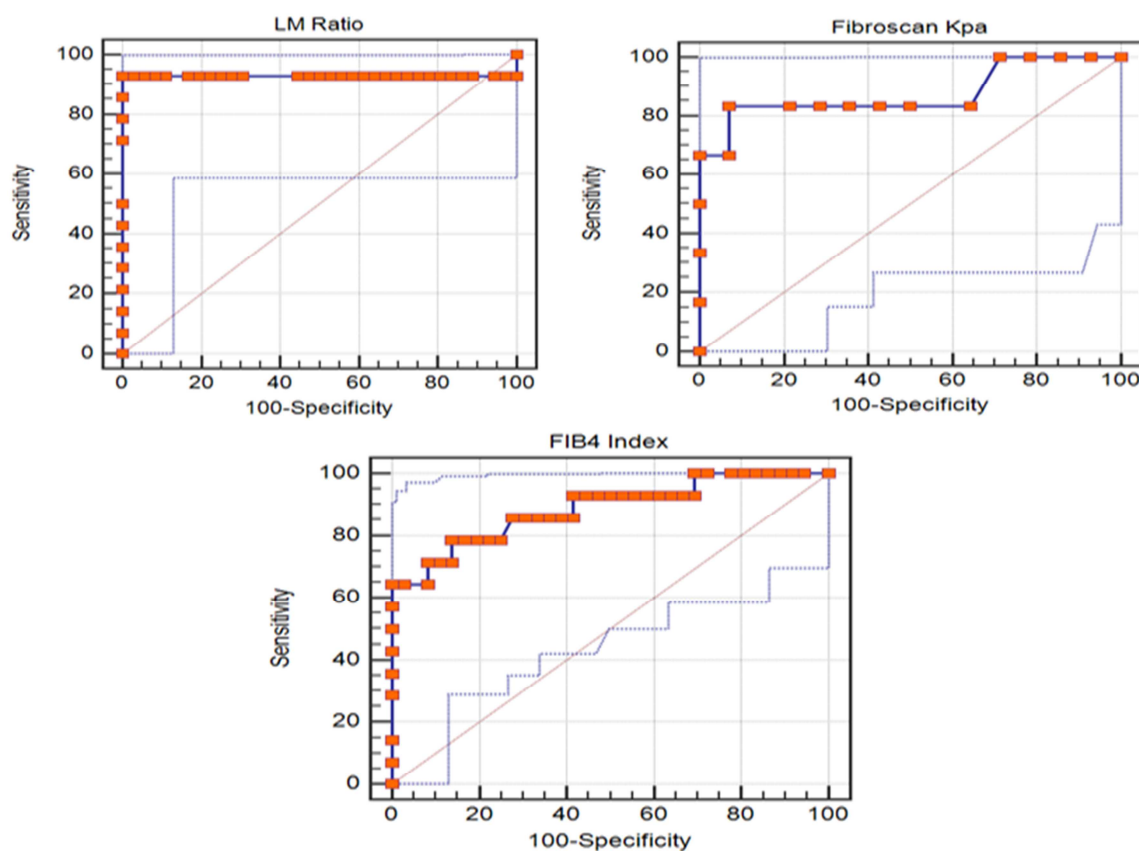| Variables	Univariate analysis		Multivariate analysis	
	OR (95% C. I)	P-value	OR (95% C. I)	P-value
Oesophageal varices	4.423 (1.153 –5.955)	0.030*	2.421 (1. 50-6.964)	0.040*
Spleen size (cm)	2.311 (1.249 – 4.275)	0.008*	1.768 (0.883-3.539)	0.108
Hemoglobin	0.380 (0.209 – 0.690)	0.001*	0.364 (0.128-1.032)	0.057
Total bilirubin	7.523 (1.270 – 14.579)	0.026*	0.685 (0.041-1.322)	0.791
Albumin	0.022 (0.002 – 0.245)	0.002*	0.005 (0.000-0.499)	0.024*
AST	1.023 (1.004 – 1.042)	0.018*	1.073 (1.004-1.147)	0.038*
Tumor size (cm)	1.273 (1.044 – 1.552)	0.017*	1.218 (0.935-1.585)	0.143
Performance status	4.091 (1.111 – 15.057)	0.074	-	-
Child score	5.012 (1.276 –9.597)	0.032*	2.748 (1.566-5.596)	0.066
LMR	2.363 (1.353-4.125)	<0.031*	1.68 (3.501 – 8.071)	0.001*
FIB-4 score	5.330 1.848 – 10.369)	0.002*	7.892 (1.323 – 9.422)	0.022*
Fibroscan values (kpa)	6.50 (3.377 – 12.512)	0.006*	5.98 (2.202– 6.480)	0.016*

Abbreviations: AST, Aspartate transaminase; C. I, confidence interval; FIB-4 score, fibrosis score 4; kpa, kilopascal; LM ratio, lymphocyte to monocyte ratio; OR, odds ratio; *significant (P ≤ 0.05).

According to the ROC curve analysis, LMR yielded the best accuracy for predicting PHLF at cutoff <3.33 [AUC = 0.940; sensitivity = 93.65%; specificity = 94.44%; positive predictive value = 86.67%; negative predictive value = 97.14%]. FIB-4 score and LSM obtained by Fibroscan had lower AUC (0.886 and 0.875) respectively "Table 4, Figure 2".

Abbreviations: PHLF, post-hepatectomy liver failure; UTI, urinary tract infection.

Figure 2. *Post-operative complications and mortality in the studied patients.*

Abbreviations: LMR, lymphocyte to monocyte ratio; FIB-4 score, fibrosis score 4; kpa, kilopascal.

Figure 3. *ROC curves for LMR, FIB-4 and Fibroscan as predictors of post-hepatectomy liver failure. LMR had the best accuracy for predicting PHLF.*

	Cutoff	Sensitivity%	Specificity%	PPV%	NPV%	AUC
LMR	<3.33	93.65	94.44	86.67	97.14	0.940
FIB-4 score	>3.94	71.43	91.67	76.9	89.2	0.886
Fibroscan values (kpa)	>15.5	83.33	92.86	83.3	92.9	0.875

Abbreviations: AUC, area under the curve; FIB-4 score, fibrosis score 4; kpa, kilopascal; LM ratio, lymphocyte to monocyte ratio; NPV, negative predictive value; PPV, positive predictive value.

4. Discussion

This study was a prospective cohort which was designed to determine the value of the LMR, FIB-4 score and LSM estimated by Fibroscan as pre-operative predictors of PHLF in Egyptian patients suffering from liver cirrhosis and HCC post HCV infection who underwent hepatectomy.

To the best of our information, this is the first study that assessed the pre-operative LMR as a predictor for PHLF. Only patients suffering from HCC related to HCV infection were enrolled in this study in order to evade possible confounding factors due to other etiologies.

In this study, a multivariate analysis revealed that pre-operative LMR, FIB-4 score and LSM using Fibroscan were independent predictors for PHLF.

The optimal pre-operative LMR cut-off value established for predicting PHLF by ROC curve analysis was <3.33 (AUC = 0.940). The mechanisms that LMR can predict PHLF could be related to a complex inflammatory response. LMR is a systemic inflammatory marker which includes lymphocytes and monocytes. Lymphocytes can protect against tumorigenesis and recurrence by inhibiting tumor cells proliferation through cytokines generation and causing cytotoxic death in cells [21]. The reduced number of lymphocyte may indicate a weak antitumor reaction leading to poor clinical outcome [22]. Another important element of immunity in human body is Monocytes, as they promote tumorigenesis by suppressing local immune systems [23]. Additionally they can differentiate into tumor-associated macrophages that promote the development of tumors, angiogenesis, invasion, and metastasis [24].

Lymphocytes and monocytes have a crucial role in the biological behavior of liver cancer, for example; the onset, differentiation, and metastases [25-27]. Several studies have showed the association between pre-operative low LMR and size, vascular invasion and staging of tumors. High LMR reflects intensive immune system anti-tumor effect, represents lymphocytosis and/or monocytopenia. On the other hand low LMR stand for the immune system depressed state. Consequently, HCC patients with high LMR have post-operative favorable outcomes, and vice versa [28].

Pre-operative LMR accurately predicts PHLF and is potentially a good indicator for selecting suitable HCC patients who will undergo hepatectomy.

As liver fibrosis and cirrhosis is detected in most of HCC patients and has a major role in the PHLF occurrence [29]. Therefore, the precise assessment of liver fibrosis and cirrhosis prior to surgery is essential. FIB-4 score and LSM estimated by Fibroscan are noninvasive methods used for the estimation of liver stiffness [12].

Our pre-operative FIB-4 score cut-off value of >3.94 (AUC=0.886 with 71.43% sensitivity and 91.67% specificity) accurately predicted PHLF in our study. This was close to the data found by Zhou et al who reported the optimal cutoff value of the FIB-4 score for predicting PHLF was 4.16 with 65.2% sensitivity and 83.3% specificity. Increased FIB-4 score value indicates advanced liver fibrosis or cirrhosis which coincided with poor liver function and poor postoperative outcome such as failure of the liver, worsening encephalopathy or ascites [30].

According to ROC curve analysis, the best cutoff value to predict PHLF for the pre-operative LSM using Fibroscan was >15.5 (kpa) (AUC= 0.875 with 83.33% sensitivity and 92.86% specificity). This was in agreement with the findings of another Egyptian study that identified LSM value ≥ 15.4 (kPa) to have the optimal cutoff value for predicting PHLF with 100% sensitivity and 100% specificity [31]. Lei et al reported that, LSM cutoff value of 14 (kPa) with 94.6% sensitivity and 67.6% specificity as the optimal cutoff for development of PHLF in Chinese patients [32].

There is a little information regarding hepatic fibrosis effect on PHLF. In the fibrotic liver, it is proposed that regeneration is a process mediated by progenitor cells, in contrast to replication of mature liver cells in the non-compromised liver. Following partial hepatectomy, liver cell regeneration impairment and subsequent hepatic dysfunction are caused by inefficient induction of mediators of cell cycle transition, necrosis of liver cell, and a marked fibrogenic response [33, 34]. Reduced activity of innate and adaptive immune system and enhanced bacterial translocation increase the vulnerability of the fibrotic liver [35].

Pre-operative FIB-4 score and LSM using Fibroscan are useful to predict PHLF in patients with HCC and should be routinely assessed in those patients who will undergo hepatectomy.

The present study has some limitations. All enrolled HCC patients had HCV liver cirrhosis in addition small sample size. So, the results of this study can't be applied to patients without chronic liver disease. Therefore, further validation is required from a large population with different etiologies.

In conclusion, the pre-operative LMR has a superior predictive ability for PHLF in patients with HCV-related HCC undergoing hepatectomy compared with FIB-4 score and LSM using Fibroscan and should be included routinely in the pre-operative workup of HCC patients being candidate

for hepatectomy.

Conflicts of Interest

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