Sequential Estimation of Serum Bilirubin and Prothrombin Time to Predict Post-Hepatectomy Events: 7-Year Study at Specialized Center

Ashraf El-Kholy A. Othman, Amr Abdelraouf, Shawkat S. Gerges, Bahaa Elwakeel, Mohammed Mogahed, Romany Y. Wilson, Zeinab Mostafa

MD, Department Of Hepatobiliopancreatic Surgery, National Hepatology & Tropical Medicine Research Institute(NHTMRI), Cairo, Egypt

Abstract

Objectives: To evaluate sequential postoperative (PO) estimation of serum bilirubin (SB) and prothrombin time percentage (PT%) as predictors for development of post-hepatectomy events (PHE) including post-hepatectomy liver failure (PHLF), other complications and mortality.

Patients & Methods: During 7-year, 410 patients underwent open abdominal hepatectomy. During 1st PO week, SB and PT% were measured daily and the extent of change of SB was calculated in relation to preoperative measures. Liver failure was defined as getting SB level of >2.9 mg/dl and prolonged PT >15 sec combined with signs of hepatic encephalopathy or hepatorenal syndrome. Study outcomes included frequency of PHE and patients were categorized as PHLF and No PHLF groups and to analyze estimated SB and PT% as predictors for development of PHE.

Results: Mean operative time was 178±27.3 min, mean amount of operative blood loss was 325±66 ml, mean number of transfused blood units was 1.6±0.6 units and mean duration of hospital stay was 4.2±1.7 days. During hospital stay and short-term follow-up, 32 patients (7.8%) developed PHLF, 134 patients (32.68%) developed other complication and 28 patients (6.83%) died with significantly higher morbidity and mortality rates among PHLF patients. Regression analysis defined calculated percentage of increase in SB on POD4 and persistently decreased PT% till POD7 as significant predictors for development of PHE, while combined extent of PT change on POD1 and high SB on POD2 as significant predictors for future development of PHLF.

Conclusion: PHE could be minimized by proper preoperative preparation, meticulous surgical procedure to minimize blood loss and shorten operative time so as to reduce blood transfusion requirements. PHE could be predicted using sequential estimation of SB and PT% since POD1. Both SB and PT% did well together as early predictors for development of PHLF and showed complementary predictive value for development of other complications and short-term mortality.

KEYWORDS: Post-hepatectomy events, sequential estimations, serum bilirubin, prothrombin time, early prediction

Introduction

Liver resection (Hepatectomy) is an important treatment modality for liver malignancies [(1)]. Hepatectomy for hepatocellular carcinoma is the best alternative option for increasing the survival of many patients with intermediate or advanced stages of liver cancer [(2)]. Moreover, major hepatectomies are widely used in curative-intent surgery for perihilar cholangiocarcinoma [(3)]. Liver resection also remains the standard treatment for liver metastases [(4)].

However, hepatectomy has high perioperative morbidity and mortality rates [(1)]. Post-hepatectomy liver failure (PHLF) is a major source of morbidity and mortality in patients undergoing liver resection [(5)]. PHLF was defined as a postoperative reduction in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions [(6)]. The International Study Group of Liver Surgery defined PHLF as development of pathological values of the international normalized ratio and bilirubin on or after postoperative day 5 (POD5) [(7)].

Multiple etiologies may underlie the development of PHLF and its subsequent additional morbidities and mortalities [(8)]. Despite of the previous finding that the risk of PHLF is not associated with surgical strategy, whether simultaneous resection or staged hepatectomy in cases with metastatic liver disease [(9)]; resection criteria should be established based on the risk of PHLF and the survival benefit from hepatectomy [(10)] and an inadequate volume of future liver remnant remains an absolute contraindication to liver resection as it correlates with surgical outcome [(11)].

PHLF is resistant to treatment and is associated with mortality, so great effort has been put in to both accurately identify patients at high risk [(5)], modify early predictors of PHLF [(12)], develop strategies that can help prevent its occurrence [(13)] and correction of modifiable causes including avoidance of sepsis, drainage of cholestasis and intraoperative judicious use of portal triad inflow occlusion to minimize the frequency of development of PHLF and maximize the survival chances [(8)].

Aim of work

The current study aimed to evaluate the outcome of open hepatectomy surgeries conducted since July 2010 in a specialized center. Moreover, the study targets to evaluate sequential PO estimation of serum bilirubin (SB) and prothrombin time percentage (PT%) as predictors for development of post-hepatectomy events.

Patients & Methods

The study protocol was approved by the Local Ethical Committee. All patients assigned for open hepatectomy, irrespective of its extent and indication, and signed a written fully informed consent were evaluated clinically and radiologically for assessment of general condition, fitness for surgery, extent of lesion, and of assigned level of hepatectomy.

Inclusion criteria included cirrhosis of Child Pugh (CP) score A or very early B with peripheral and/or exophitic lesions not necessitating major resection and lesions in non-cirrhotic patients that required hepatectomy with the remaining liver was >30% in cases of major hepatectomies, after assessment with CT scan volumetry. Exclusion criteria included cirrhosis of CP Score late B and more, bad general condition, major hepatectomies with remaining liver <40% of normal liver or <50% of cirrhotic liver and hepatecomies in children.

All included patients underwent clinical and laboratory evaluation of liver damage parameters and function parameters. Serum bilirubin and PT% were measured daily during 1st postoperative (PO) week. To obtain PT% expression, a saline dilution curve was constructed with normal pool plasma and the patient's result was expressed as the percentage of normal plasma yielding the same PT in seconds [(14)]. The extent of change of SB was calculated in relation to preoperative measures as follows: Estimated levels at PO day (POD)/preoperative level multiplied by 100.

Liver failure was defined as getting SB level of >2.9 mg/dl, prolonged PT >15 sec [(15, 16)], and increased plasma ammonia levels >100 µmol/L combined with signs of hepatic encephalopathy or hepatorenal syndrome, requiring intensive care [(17)].

Study outcome

1. **Primary outcome** is the frequency of development of PO events including PHLF, other PO complications and mortality.
2. **Secondary outcome** included evaluation of changes of SB and PT% throughout POD1-7 in studied patients as a total and categorized according to development of PHLF as PHLF group and No PHLF group and to analyze estimated SB and PT% and their percentage of change as predictors for development of PO events.

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using paired t-test and One-way ANOVA with post-hoc Tukey HSD Test. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors for development of PO events. Cox regression analysis was applied to the chosen predictors to determine the cumulative risk for development of PO events. Statistical analysis was conducted using the IBM SPSS Statistics (Version 23, 2015; IBM Co., Armonk, NY, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Throughout the 7-year duration 456 patients with liver mass necessitated resection were evaluated; 46 patients were excluded and 410 patients were included in the study and underwent hepatectomy (Fig. 1). The inclusion and preoperative data are shown in table 1.

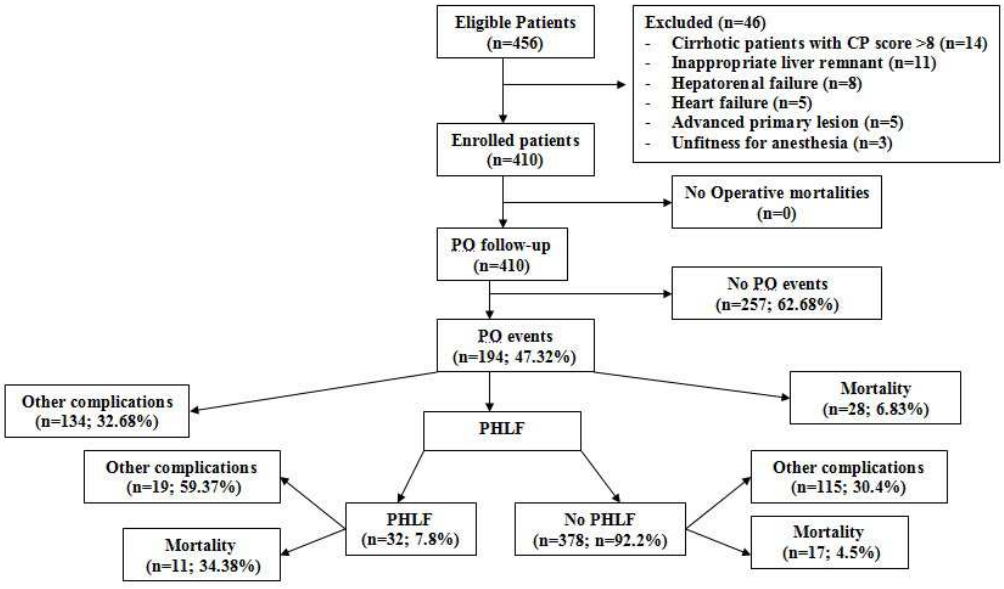

Fig. (1): Flow sheet of outcome of studied patients

Table (1): Patients' inclusion criteria

Criteria			Findings
Age (years)	Categories	<40	26 (6.35%)
		40-50	24 (5.85%)
		51-60	241 (58.8%)
		>60	119 (29%)
	Mean total age		56.5±7.64 (32-68)
Gender	Males		269 (65.61%)
	Females		141 (34.39%)

Weight (kg)	80.58±12.66
Height (cm)	170±3.21
Body mass index (kg/m^2)	27.89±4.35

Data are presented as numbers & mean±SD; percentages & ranges are in parenthesis

All surgeries were conducted uneventfully within a mean operative time of 178±27.3 min. Mean amount of operative blood loss was 325±66 ml and mean number of transfused blood units was 1.6±0.6 units. Mean of total hospital stay was 4.2±1.7 days. During hospital stay and short-term follow-up, 32 patients developed PHLF (PHLF group) for a frequency 7.8%, while 378 patients completed their short-term follow-up free of PHLF (No PHLF group). Patients of PHLF group had significantly (p=0.001) longer operative time, showed significantly (p=0.033) more intraoperative blood loss and consumed significantly more blood units (p=0.024) than patients of No PHLF group (Table 2). Duration of PO hospital stay was significantly (p=0.016) longer in patients of PHLF group than in No PHLF group. Pathological diagnosis of excised liver assured primary hepatic neoplastic lesion in 315 specimens (76.83%) and metastatic lesions in 95 specimens (23.17%) as shown in table 3.

Table (2): Operative data of studied patients

Data	No PHLF (n=378)	PHLF (n=32)	P value
Operative time (min)	167.2±22.8	191.3±26.7	0.001
Intraoperative morbidities or mortality	0	0	
Operative blood loss (ml)	310.9±68.4	344.6±60.7	0.033
Number of transfused blood units	1.8±0.7	1.4±0.5	0.024
Total hospital stay (days	3.8±1.7	4.8±1.7	0.016

Data are presented as mean±SD

Table (3): Final pathological diagnosis after examination of the excised specimen

Source of the lesion	Pathological diagnosis	Number (%)
Primary lesion	Hepatocellular carcinoma	162 (41.95%)
	Hepatoma	78 (19.03%)
	Hilar cholangiocarcinoma	32 (7.8%)
	Chronic sclerosing cholangitis	15 (3.66%)
	Cholangiocellular carcinoma	7 (1.71%)
	Cystadenoma	3 (0.73%)
	Focal nodular hyperplasia	8 (1.95%)
Metastatic lesions		95 (23.17%)

Data are presented as numbers; percentages are in parenthesis

During hospital stay and short-term follow-up, 134 patients developed 233 PO complication other than PHLF (Table 4) for a short-term complication rate of 32.68%; 19 patients of PHLF group developed 64 PO morbidities other than PHLF for a frequency of 3.37 morbidities/ patient and a short-term complication rate of 59.37%.

On the other hand, 115 patients of No PHLF group developed 169 morbidities other than PHLF for a frequency of 1.47 morbidities/ patient and a short-term complication rate of 30.4%. The short-term complication rate was significantly (p=0.005) higher among patients of PHLF group than patients of No PHLF group (Table 5, Fig. 2).

Table (4): Immediate and short-term PO complications encountered in patients of both groups

Complication	No PHLF (n=378)	PHLF (n=32)	Total (n=410)
Liver abscess/ necrosis	7 (1.85%)	2 (6.25%)	9 (2.2%)
Cholangitis	11 (2.91%)	3 (9.38%)	14 (3.41%)
Bile leakage	9 (2.38%)	2 (6.25%)	11 (2.68%)
Ascites	17(4.5%)	3 (9.38%)	20 (4.88%)
Peritonitis	14 (3.7%)	3 (9.38%)	17 (4.15%)
Bleeding or repeated bleeding	22 (5.8%)	10 (31.25%)	32 (7.8%)
Wound sepsis	21 (5.56%)	9 (28.13%)	30 (7.32%)
Wound rupture	11 (2.9%)	5 (15.63%)	16 (3.9%)
Renal failure	8 (2.11%)	4 (12.5%)	12 (2.93%)
Urinary tract infection	13 (3.44%)	6 (18.75%)	19 (4.63%)
Cardiac failure	6 (1.59%)	1 (3.13%)	7 (1.71%)
Pulmonary failure	7 (1.85%)	3 (9.38%)	10 (2.77%)
Pneumonia	6 (1.59%)	2 (6.25%)	8 (1.95%)
Pleural fluid	11 (2.91%)	2 (6.25%)	13 (3.17%)
Delirium	6 (1.59%)	9 (28.13%)	15 (3.66%)

Data are presented as numbers; percentages are in parenthesis

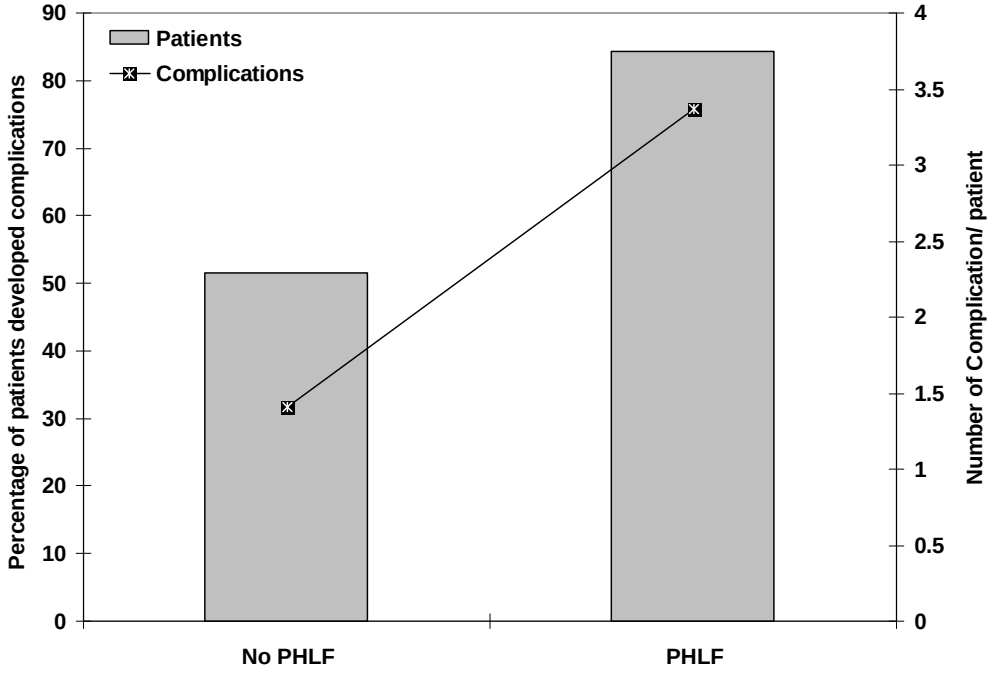

Fig. (2): Percentage of patients and number of complications other than PHLF per patient among patients of both groups

Thirty-five patients required repeated laparotomy for management of bleeding or peritonitis for a frequency of 8.54%; 30 patients (7.94%) in No PHLF group and 5 patients in PHLF group (15.63%) with significantly (p=0.027) higher frequency of repeated laparotomy in PHLF group. Forty-four patients (10.73%) required treatment in ICU; 10 patients for management of respiratory failure, 8 patients for management of pneumonia, 7 patients for management of heart failure and 19 patients for management after re-laparotomy. Seven patients (21.88%) of PHLF group and 37 patients (10.08%) in No PHLF group required treatment in ICU with significantly (p=0.010) higher frequency among PHLF patients. Unfortunately, 28 patients (6.83%) died during hospital stay and short-term follow-up period; 11 patients (34.38%) in PHLF group and 17 patients (4.5%) in No PHLF group with significantly (p=0.00001) higher mortality rate among PHLF patients (Table 5, Fig. 3).

Table (5): Immediate and short-term PO events encountered in patients of both groups

			No PHLF (n=378)	PHLF (n=32)	Total (n=410)
PO morbidity	No		263 (69.6%)	13 (40.63%)	276 (67.32%)
	Yes	Number of patients	115 (30.4%)	19 (59.37%)	134 (32.68%)
		Number of morbidities	169	64	233
		Frequency/patient	1.47	3.37	0.57
Treatment in intensive care unit			37 (10.08%)	7 (21.88%)	44 (10.73%)
Repeated laparotomy			30 (7.94%)	5 (15.63%)	35 (8.54%)
Mortality			17 (4.5%)	11 (34.38%)	28 (6.83%)

Data are presented as numbers; percentages are in parenthesis

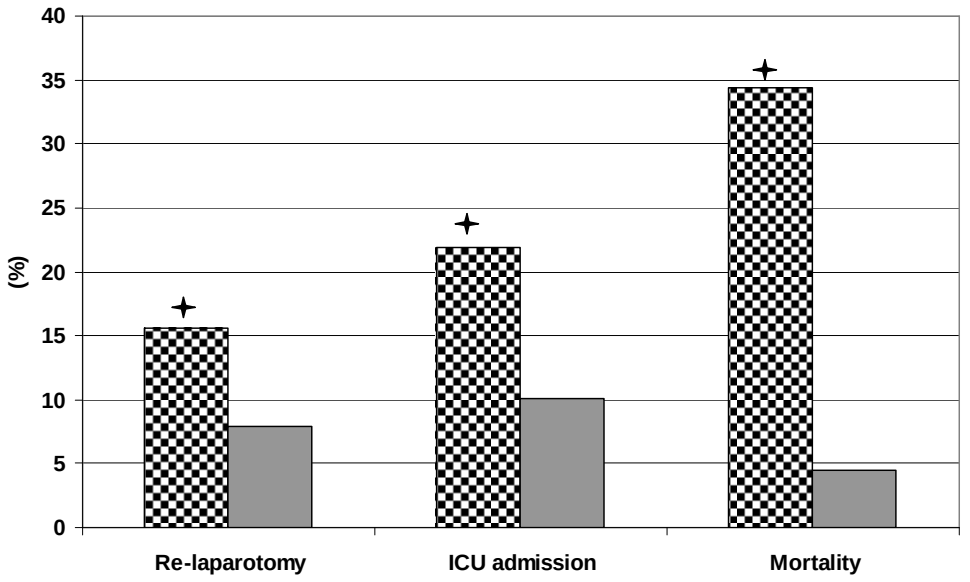

Fig. (3): Patients' distribution according to development of PO events in both groups (✦ significant difference)

Throughout the 1st week PO, all patients showed deteriorated liver functions manifested as increased levels of SB that was significantly higher in comparison to preoperative SB since POD1 till POD4 to be non-significantly higher on POD5 and POD6 and decreased significantly on POD7 (Fig. 4); such deterioration of the excretory function of liver remnant was significantly higher in patients who developed PHLF compared to patients of No PHLF group (Table 6).

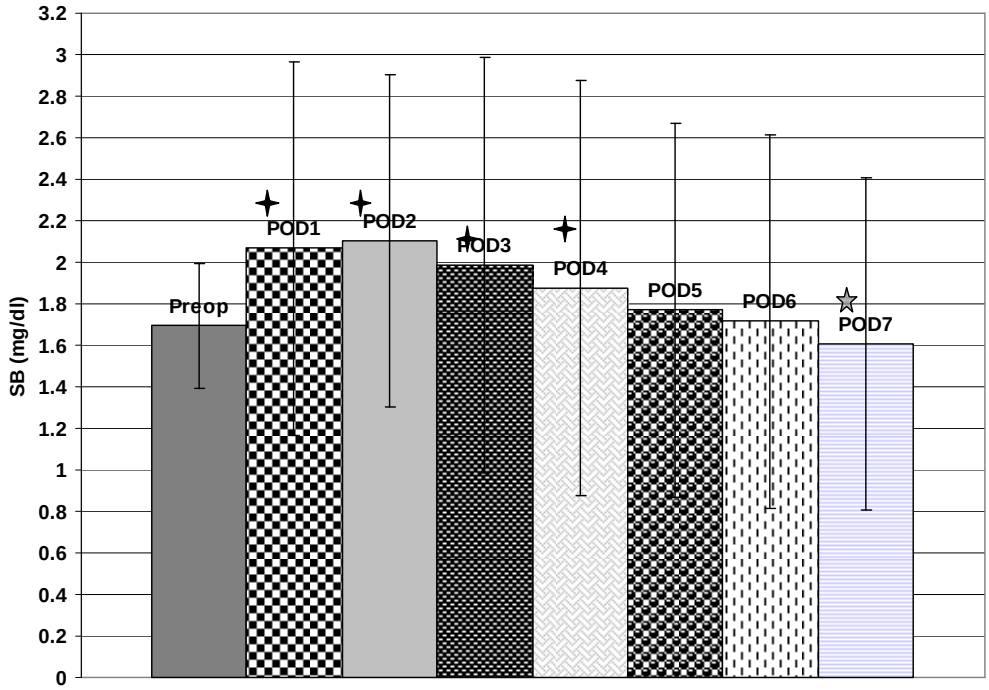

Fig. (4): Mean(±SD) SB levels estimated in studied patients during 1st week PO (✦ significantly higher; ☆ significantly lower versus preop.)

Moreover, the percentage of patients' PT in relation to control time showed gradual deterioration reaching the lowest level on POD4 and re-increase reaching its maximum on POD7; such deterioration of the synthetic function of liver remnant was significantly higher in patients who developed PHLF compared to patients of No PHLF group (Table 6, Fig. 5).

Table (6): Serum bilirubin and percentage of prothrombin time in relation to control time estimated throughout 1st week PO in comparison to preoperative levels in both groups

Parameter			Preop.	POD1	POD2	POD3	POD4	POD5	POD6	POD7
SB	No PHLF	Level	1.65±0.28	1.83±0.28	1.9±0.3	1.7±0.3	1.6±0.28	1.5±0.25	1.5±0.25	1.4±0.23
		%		11.8±10.8	16.1±12.2	6.6±25.2	-0.21±24	-5.7±22	-8.5±22	-14.8±20
	PHLF	Level	2.3±0.22	5±0.7	4.58±0.72	5.4±0.76	5.1±0.7	4.88±0.6	4.7±0.6	4.4±0.56
		%		118±33	100±32	136±35	125±32.7	114±31	107±30	95±29.6
	Total	Level	1.7±0.3	2.07±0.9	2.1±0.8	1.96±1	1.9±1	1.78±0.9	1.7±0.9	1.6±0.8
		%		19.9±31	22.5±26.4	16.5±43	9.5±41.4	3.6±39	0.41±38	-6.3±36
PT	No PHLF	Level	92.2±8.7	91±8.3	86.9±8.5	78.5±8	77.2±8.4	81.5±8.2	82.3±8	87.6±8.1
		%		-1.2±2.8	-5.6±4.9	-14.4±9	-15.9±9	-11±9.5	-10.3±9.4	-4.9±2.3
	PHLF	Level	91.9±10	44.1±8	71.3±11	59±10	53.5±9.1	49.2±8.6	65.7±10.8	46.9±8.3
		%		-51.6±9	-22.1±12	-35.4±11	-41.4±10	-46±9	-28±12	-48.5±10
	Total	Level	90.9±12.1	85.9±17.6	84.7±11.9	75.9±11.8	74.3±12.8	77.8±14.4	80±11.7	83±16
		%		-5.8±14.7	-6.5±7.8	-16±11	-18±11.9	-14±13.6	-11.4±11	-8.8±12

Data are presented as numbers & mean±SD; percentages & ranges are in parenthesis; SB: Serum bilirubin; PT: Prothrombin time; PHLF: Post-hepatectomy liver failure; Preop.: Preoperative; POD: Postoperative day; %: Percentage of change in relation to preoperative level

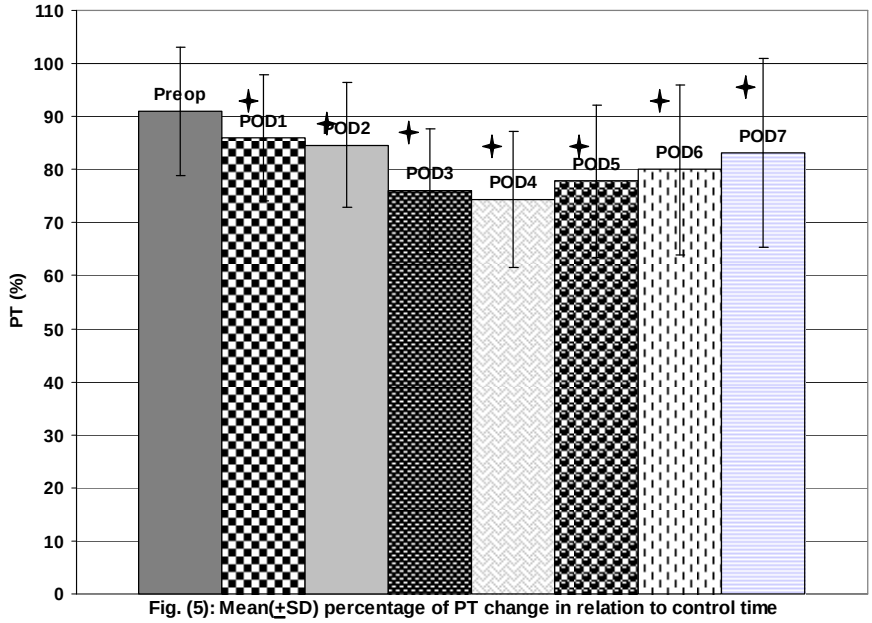

Fig. (5): Mean(±SD) percentage of PT change in relation to control time estimated in studied patients during 1st week PO (+ significantly lower versus preop.)

Regression analysis defined elevated SB level on POD2 as a persistently significant predictor for development of PHLF, while elevated SB level on POD3 was defined as a predictor for development of complication and mortality. Calculated percentage of increase in SB on POD4 in relation to preoperative SB levels was defined as the only significant predictor for development of PO events; PHLF, complications and mortality. On the other hand, persistently decreased PT% till POD7 was found as the significant predictor for development of PO events; PHLF, complications and mortality; while high extent of change of PT% on POD1 was a significant predictor for development of PHLF, and persistently high extent of change PT% in relation to preoperative PT% till POD7 was found as the only significant predictor for development of complications and mortality (Table 7).

Table (7): Regression analysis of studied estimates of SB and PT% throughout 1st week PO as predictor for development of PO events

	SB			Extent of change			PT%			Extent of change		
	Variable	β	p	Variable	β	p	Variable	β	p	Variable	β	p
PHLF												
Model 1	POD2	0.951	0.0001	POD4	0.898	0.0001	POD7	0.691	0.0004	POD1	0.915	0.0001
Model 2	POD2	0.576	0.0003	POD4	0.717	0.0003	POD7	1.253	0.0001	POD1	0.850	0.0002
	POD3	0.401	0.0005	POD7	0.216	0.0008	Preop.	0.851	0.0002	POD6	0.121	0.0007
Model 3	POD2	0.447	0.0004	POD4	0.680	0.0004	POD7	0.805	0.0002	POD1	0.429	0.0006
	POD3	0.299	0.0008	POD7	0.171	0.0009	Preop.	0.888	0.0001	POD6	0.139	0.0008
	POD4	0.244	0.0009	POD3	0.090	0.034	POD1	0.478	0.0006	POD7	0.436	0.0009
Complications												
Model 1	POD3	0.159	0.001	POD3	0.134	0.007	POD7	0.169	0.001	POD7	0.158	0.001
Mortality												

Model 1	POD3	0.304	0.0007	POD4	0.328	0.0009	POD7	0.171	0.001	POD7	0.269	0.0008
Model 2							POD7	0.362	0.0007			
							Preop.	0.289	0.0008			
Model 3							POD7	0.476	0.0004			
							Preop.	2.145	0.033			
							POD6	0.225	0.048			

Verification of these parameters for prediction of PO events, defined the high SB levels estimated on POD2 as significant (β: 0.951, p=0.00001) positive predictor and the extent of change of PT on POD1 as a significant (β: -0.377, p=0.0005) negative predictor for future development of PHLF. Cumulative hazard function analysis defined increased SB levels by >75% of preoperative SB level as a point for increased likelihood ratio for development of PHLF (Fig. 6).

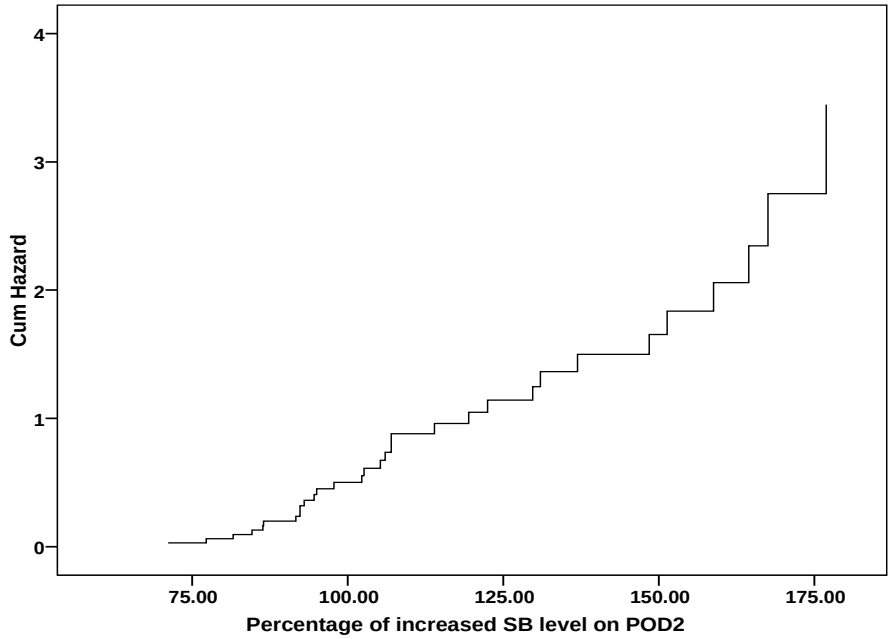

Fig. (6): Hazard Function of percentage of increased SB level on POD2 for development of PHLF among studied patients

Regression analysis defined prolonged PT manifested as decreased PT% reaching maximum on POD7 as negative predictor (β: -0.168, p=0.001) for development of complications other than PHLF among studied patients with cumulative risk for developing complication was increasing by decreased PT% by >80% (Fig. 7).

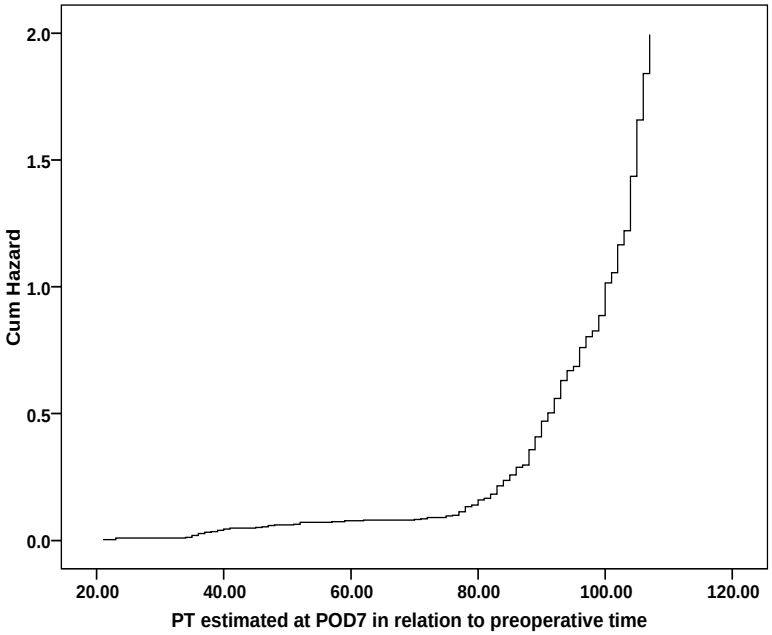

Fig. (7): Hazard Function of prolonged PT on POD7 for development of complication among studied patients

The percentage of elevation of SB on POD4 was defined as positive significant (β: 0.328, p=0.0007) predictor for mortality during short-term follow-up period with increasing cumulative hazard for mortality after 100% increase of SB relative to preoperative SB level (Fig. 8).

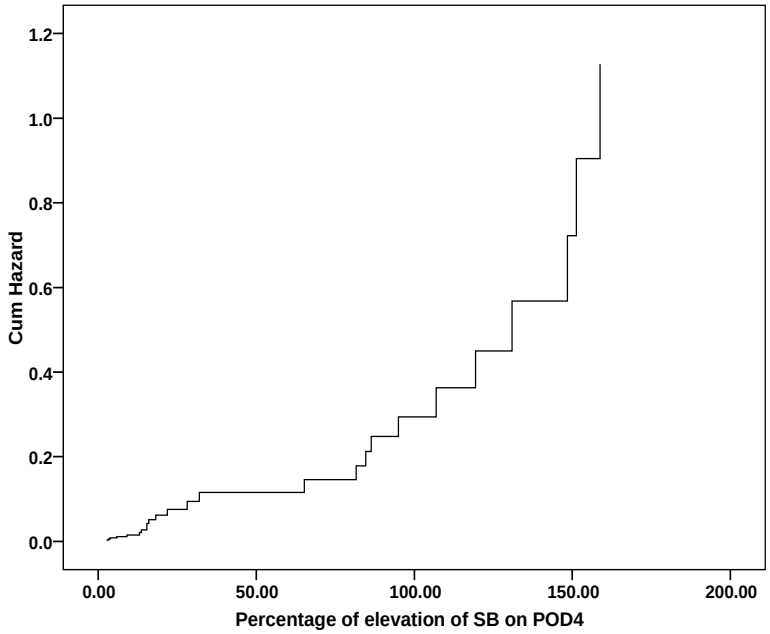

Fig. (8): Hazard Function of percentage of elevated SB for mortality among studied patients

Discussion

Throughout 7-year study, 410 patients were subjected to open hepatectomy for various extents according to preoperative imaging studies; 315 patients had primary

hepatic malignancy and 95 patients had metastatic lesions. All surgeries were conducted uneventfully within a mean operative time of about 6.7 hr with mean amount of operative blood loss of about 1015 ml and mean number of transfused blood units of about 5.1 units, and mean hospital stay was about 19 days. Similarly, **Rössler et al.** [18] out of their series of hepatectomies found surgery lasted for about 7 hours and mean hospital stay was about 12 days. Also, **Kuramitsu et al.** [19] reported that the average hospital stay without PHLF was about 15 days, which extended with development of PHLF and with increasing its grades.

Unfortunately, the frequency of PHLF has varied greatly among studies since a clear definition of PHLF has been lacking [4]. During hospital stay and short-term follow-up of currently studied patients, 32 patients developed PHLF for a frequency 7.8%. In line with such figure, **Vibert et al.** [20], **Schnitzbauer et al.** [21] and **Yadav et al.** [22] reported that the incidence of PHLF was 7%, 7.4% and ranging between 3 and 8 %, respectively. On the other hand, **Narita et al.** [4] documented that the frequency of PHLF is ranging from 1% to 16%, while **Dumitrascu et al.** [3]**, Schadde et al**. [23] and **Nishio et al.** [24] reported clinically relevant PHLF in 24%, 21.5% and 14% of their series, respectively. The highest reported figure for development of PHLF was 55.1% by **Uchida et al.** [1].

Patients of PHLF group had consumed significantly longer theater time, developed significantly more intraoperative blood loss and consumed significantly more blood units than patients free of PHLF. Similarly, **Dumitrascu et al.** [3] found the number of blood units >3 is an independent prognostic factor for clinically relevant PHLF and **Kuramitsu et al.** [19] reported that prolonged operation time was significantly associated with high incidence of PHLF.

During one-week PO, all patients showed significantly higher SB with significant prolongation of PT manifested as significantly decreased PT% compared to preoperative estimates and these deteriorations were significantly evident in PHLF patients compared to patients of No PHLF group. Similarly, **Lin et al.** [25] detected significantly higher PO serum total bilirubin, international normalized ratio, and peritoneal drainage fluid at the 3rd and 5th PO day in PHLF than non-PHLF patients.

Concerning PO events other than PHLF, 134 patients (32.68%) developed PO complications with significantly higher frequency among PHLF than No PHLF patients. Similarly, **Skrzypczyk et al.** [26] found the 3-month major morbidity rate was 16.5% and **Menclová et al.** [27] reported an incidence of bile leakage of 21% after hepatectomy. Short-term PO mortality rate was 6.83% with significantly higher mortality rate among PHLF patients than No PHLF patients (34.38% vs. 4.5%); in line with such mortality rate, **Skrzypczyk et al.** [26] and **Kim et al.** [28] reported operative mortality of 4.4% and 4.7%, respectively, after hepatectomy. Also, **Stoffels et al.** [29] found the 30-day mortality and overall in-hospital mortality after hepatectomy were 4.95 and 8.91%, respectively.

Regression analysis for sequentially estimated levels of SB and PT%, defined POD2 estimated SB as significant positive predictor and extent of PT% change on POD1 as significant negative predictor for future development of PHLF, these findings spot light on the diagnostic value of early disturbance of SB and PT for prediction of an on-coming event and the complementary diagnostic value of both parameters for such prediction. In support of such assumption, prolonged PT reaching maximum on POD7 was defined as negative predictor for development of complications other than PHLF and the percentage of elevation of SB on POD4 was defined as positive significant predictor for mortality during short-term follow-up period. These data illustrated the diagnostic value of sequential estimations, the

complementary diagnostic value of both parameters and applicability for both parameters to predict post-hepatectomy events up to prediction of mortality. In line with the these findings and assumptions, **Kim et al.** [28] reported that PT <65% and SB ≥38 μmol/L on POD 5 showed the only significant difference as compared with "50-50" criterion for post-hepatectomy mortality prediction. Also, **Kudo et al.** [30] found PT%, TB, and direct bilirubin were the best predictors in patients with both early liver failure and mortality from recurrence-free liver failure and PT% alone was the best predictor of both events with area under ROC curves of 0.70 and 0.81, respectively. Recently, **Nakagawa et al.** [31] found high SB on POD1 in combination with low platelet count and another three operative findings as independent predictors for biliary leakage.

Conclusion

Post-hepatectomy events, despite being frequently encountered, could be minimized by proper preoperative preparation, meticulous surgical procedure to minimize operative blood loss and shorten operative time so as to reduce blood transfusion requirements. Post-hepatectomy events could be predicted using sequential estimation of SB and PT% since first day PO. Both SB and PT% did well together as early predictors for development of PHLF and showed complementary predictive value for development of other complications and short-term mortality

References

1. Uchida Y, Furuyama H, Yasukawa D, Nishino H, Ando Y, Hata T, Machimoto T, Yoshimura T: Hepatectomy Based on Future Liver Remnant Plasma Clearance Rate of Indocyanine Green. HPB Surg. 2016;2016:7637838. doi: 10.1155/2016/7637838.
2. Gruttadauria S, Tropea A, Pagano D, Guarini A, Liotta R, Ling T, Tuzzolino F, Luca A, Vizzini G, Gridelli B: Mini-Invasive Approach Contributes to Expand the Indication for Liver Resection for Hepatocellular Carcinoma Without Increasing the Incidence of Posthepatectomy Liver Failure and Other Perioperative Complications: A Single-Center Analysis. J Laparoendosc Adv Surg Tech A. 2016; 26(6):439-46.
3. Dumitrascu T, Brasoveanu V, Stroescu C, Ionescu M, Popescu I: Major hepatectomies for perihilar cholangiocarcinoma: Predictors for clinically relevant postoperative complications using the International Study Group of Liver Surgery definitions. Asian J Surg. 2016; 39(2):81-9.
4. Narita M, Oussoultzoglou E, Bachellier P, Jaeck D, Uemoto S: Post-hepatectomy liver failure in patients with colorectal liver metastases. Surg Today. 2015; 45(10):1218-26.
5. Lafaro K, Buettner S, Maqsood H, Wagner D, Bagante F, Spolverato G, Xu L, Kamel I, Pawlik TM: Defining Post Hepatectomy Liver Insufficiency: Where do We stand? J Gastrointest Surg. 2015; 19(11):2079-92.
6. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011; 149: 713-724.
7. Brooke-Smith M, Figueras J, Ullah S, Rees M, Vauthey JN, Hugh TJ, Garden OJ, Fan ST, Crawford M, Makuuchi M, Yokoyama Y, Büchler M, Weitz J, Padbury

R: Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB (Oxford). 2015; 17(1):46-51.
8. Garcea G1, Maddern GJ: Liver failure after major hepatic resection. J Hepatobiliary Pancreat Surg. 2009;16(2):145-55.
9. Iguchi K, Hatano E, Yamanaka K, Tanaka S, Taura K, Uemoto S: Validation of the Conventional Resection Criteria in Patients with Hepatocellular Carcinoma in Terms of the Incidence of Posthepatectomy Liver Failure and Long-Term Prognosis. Dig Surg. 2015; 32(5):344-51.
10. Patrono D, Paraluppi G, Perino M, Palisi M, Migliaretti G, Berchialla P, Romagnoli R, Salizzoni M: Posthepatectomy liver failure after simultaneous versus staged resection of colorectal cancer and synchronous hepatic metastases. G Chir. 2014; 35(3-4):86-93.
11. Pulitano C, Crawford M, Joseph D, Aldrighetti L, Sandroussi C: Preoperative assessment of postoperative liver function: the importance of residual liver volume. J Surg Oncol. 2014; 110(4):445-50.
12. Dong J, Zhang XF, Zhu Y, Ma F, Liu C, Wang WL, Liu XM, Wang B, Lv Y: The value of the combination of fibrosis index based on the four factors and future liver remnant volume ratios as a predictor on posthepatectomy outcomes. J Gastrointest Surg. 2015; 19(4):682-91.
13. Eshkenazy R, Dreznik Y, Lahat E, Zakai BB, Zendel A, Ariche A: Small for size liver remnant following resection: prevention and management. Hepatobiliary Surg Nutr. 2014; 3(5):303-12.
14. Annie Robert, Olivier Chazouille` re: Prothrombin Time in Liver Failure: Time, Ratio, Activity Percentage, or International Normalized Ratio? Hepatology, 1996;24:1392-4.
15. Lee WM. Acute liver failure. Am J Med. 1994;96(suppl):2S–9S.
16. Fingerote RJ, Bain VG. Fulminant hepatic failure. Am J Gastroenterol. 1993;88:1000–1010.
17. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J: Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology. 2007; 46(6):1844-52.
18. Rössler F, Sapisochin G, Song G, Lin YH, Simpson MA, Hasegawa K, Laurenzi A, Sánchez Cabús S, Nunez MI, Gatti A, Beltrame MC, Slankamenac K, Greig PD, Lee SG, Chen CL, Grant DR, Pomfret EA, Kokudo N, Cherqui D, Olthoff KM, Shaked A, García-Valdecasas JC, Lerut J, Troisi RI, De Santibanes M, Petrowsky H, Puhan MA, Clavien PA: Defining Benchmarks for Major Liver Surgery: A multicenter Analysis of 5202 Living Liver Donors. Ann Surg. 2016; 264(3):492-500.
19. Kuramitsu K, Fukumoto T, Kobayashi T, Fukushima K, Okimoto S, Iwasaki T, Tominaga M, Zen Y, Ohdan H, Ku Y: The Incidence of Posthepatectomy Liver Failure Defined by the International Study Group of Liver Surgery among Living Donors. J Gastrointest Surg. 2016; 20(4):757-64.
20. Vibert E, Pittau G, Gelli M, Cunha AS, Jamot L, Faivre J, Castro Benitez C, Castaing D, Adam R: Actual incidence and long-term consequences of posthepatectomy liver failure after hepatectomy for colorectal liver metastases. Surgery. 2014; 155(1):94-105.
21. Schnitzbauer AA, Mönch C, Meister G, Sonner FM, Bechstein WO, Ulrich F: Incidence of posthepatectomy liver failure and biliary leakage : A cohort study. Chirurg. 2015; 86(8):776-80.

22. Yadav K, Shrikhande S, Goel M: Post hepatectomy liver failure: concept of management. J Gastrointest Cancer. 2014; 45(4):405-13.
23. Schadde E, Raptis DA, Schnitzbauer AA, Ardiles V, Tschuor C, Lesurtel M, Abdalla EK, Hernandez-Alejandro R, Jovine E, Machado M, Malago M, Robles-Campos R, Petrowsky H, Santibanes ED, Clavien PA: Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg. 2015; 262(5):780-6.
24. Nishio T, Taura K, Koyama Y, Tanabe K, Yamamoto G, Okuda Y, Ikeno Y, Seo S, Yasuchika K, Hatano E, Okajima H, Kaido T, Tanaka S, Uemoto S: Prediction of posthepatectomy liver failure based on liver stiffness measurement in patients with hepatocellular carcinoma. Surgery. 2016; 159(2):399-408.
25. Lin XJ, Yang J, Chen XB, Zhang M, Xu MQ: The critical value of remnant liver volume-to-body weight ratio to estimate posthepatectomy liver failure in cirrhotic patients. J Surg Res. 2014; 188(2):489-95.
26. Skrzypczyk C, Truant S, Duhamel A, Langlois C, Boleslawski E, Koriche D, Hebbar M, Fourrier F, Mathurin P, Pruvot FR: Relevance of the ISGLS definition of posthepatectomy liver failure in early prediction of poor outcome after liver resection: study on 680 hepatectomies. Ann Surg. 2014; 260(5):865-70
27. Menclová K, Bělina F, Pudil J, Langer D, Ryska M: Bile leakage after liver resection: A retrospective cohort study. Rozhl Chir. 2015; 94(12):516-21.
28. Kim SH, Kang DR, Lee JG, Kim DY, Ahn SH, Han KH, Chon CY, Kim KS: Early predictor of mortality due to irreversible posthepatectomy liver failure in patients with hepatocellular carcinoma. World J Surg. 2013; 37(5):1028-33.
29. Stoffels B, Enkirch SJ, Websky MW, Vilz TO, Pantelis D, Manekeller S, Schäfer N, Kalff JC: Posthepatectomy Liver Failure in Extended Liver Resections: An Overview Based on a Retrospective Single-Centre Analysis. Zentralbl Chir. 2016; 141(4):405-14.
30. Kudo A, Igari T, Kumagai J, Ban D, Tanaka S, Irie T, Noguchi N, Nakamura N: A Simple Index to Predict Liver Functional Reserve after Hepatectomy. Hepatogastroenterology. 2014; 61(131):712-6.
31. Nakagawa K, Tanaka K, Nojiri K, Sawada Y, Kumamoto T, Ueda M, Minami Y, Mochizuki Y, Morioka D, Kubota T, Kamiya N, Yoshida K, Yonemoto N, Endo I: Predictive factors for bile leakage after hepatectomy for hepatic tumors: a retrospective multicenter study with 631 cases at Yokohama Clinical Oncology Group (YCOG). J Hepatobiliary Pancreat Sci. 2017; 24(1):33-41. doi: 10.1002/jhbp.411.