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Prediction of Effective Percutaneous Transhepatic Biliary Drainage in Patients with Hepatocellular Carcinoma

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1. Abstract

1.1. Purpose

Percutaneous transhepatic biliary drainage (PTBD) does not always lead to a reduction in serum total bilirubin level (TBil) in patients with hepatocellular carcinoma who have Hepatitis B virus-related cirrhosis and obstructive jaundice. We aimed to develop a model for pre-PTBD prediction of post-procedural TBil decrease in these patients.

1.2. Materials and Methods

Databases of four teaching hospitals were retrospectively searched (reference period: January 2010 to December 2018) and baseline features of eligible patients were extracted. Any decrease in TBil after PTBD, lowest post-PTBD TBil <5 mg/dL, 3 mg/dL, and 2 mg/dL were each taken as standard of effectiveness for computation of its own predictive nomogram. Lasso regression model was used for data dimension decrease and feature selection. Multivariable logistic regression analysis was used to develop nomograms. The performance of each nomogram was internally assessed with respect to its calibration, discriminative ability, and clinical usefulness.

1.3. Results

138 patients were included. Time-to-treatment, Model for End-Stage Liver Disease (MELD) score, platelet count, and portal vein thrombosis (PVT) were predictors in the nomogram for any decrease in

TBil; international normalized ratio, MELD score, platelet count, and PVT were predictors for a decrease to <5 mg/dL; MELD score, cholinesterase level (CHE), platelet count, and PVT were predictors for a decrease to 3 mg/dL; and MELD score, CHE, platelet count, and prealbumin level were predictors for a decrease to 2 mg/dL. Decision curve analysis demonstrated the clinical usefulness of the nomograms.

1.4. Conclusion

These models may help inform clinical decision-making for performing PTBD procedures.

2. Introduction

In patients with hepatocellular carcinoma (HCC) and underlying Hepatitis B virus (HBV)-related cirrhosis, clinically-successful relief of obstructive jaundice has been shown to improve survival and quality of life.[1-14] However, effective lowering of serum level of total bilirubin (TBil) is achieved in only a fraction of well-drained patients (Supplementary Table 1 & 2), and because this condition is relatively uncommon (Supplementary Table 1), the correlates of the outcomes of decompression are not well characterized [1-24]. Percutaneous transhepatic biliary drainage (PTBD), one of the main methods of decompression, is an invasive procedure not without risks, as well as inconveniences and discomforts inherent to long-term drainage [17-24]. Therefore, identification of factors that may help predict the effectiveness of PTBD assessed by post-procedural TBil level, is of much clinical relevance. Only patients with HBV-related cirrhosis were included in this study because HCC occurring in these patients showed more aggressive behavior [25,26]. Moreover, this variable of disease background would constitute a potentially strong confounder that called for a dedicated study. We retrospectively reviewed clinical data of patients who were well-drained by means of PTBD at four teaching hospitals [17,21] and tried to build models to predict whether TBil would be lowered at all or lowered to under 5 mg/dL, 3 mg/dL, or 2 mg/dL, 4 weeks after PTBD. These thresholds have been commonly used as endpoints in similar studies [1-24].

Supplementary Table 1. Features of previously reported HCC patients with obstructive jaundice.

Reports	Prevalence rate of obstructive jaundice in HCC patients	Portal vein tumor thrombosis	Total bilirubin (mg/dL)	Time to treatment [mean±SD (days)]
Ueda M, et al. 1994.[9]	1.66% (9/542)	-	-	-
Jongkyoung Choi, et al. 2013.[6]	60 cases reported, 50 were previously treated	35/60 (58.3%) overall, 20/39 (51.3%) in successful group, and 15/21 (71.4%) in unsuccessful group.	17.0±9.8 overall; 16.0±9.6 in successful patients, and 18.9±10.1 in unsuccessful	-
Joon Woo Lee, et al. 2002.[4]	22 cases reported	-	14.2±6 in good, and 25.9±13.8 in poor response	29.0±23.0 in good, and 43.0 ± 40.2 in bad response
Yang-Gun Suh, et al. 2014.[3]	2.20% (63/2861)	37/63 (58.7%) overall, 28/48 (58.3%) in unsuccessful group, and 9/15 (60%) in successful group	10.2 (2.2–28.5) in unsuccessful patients; 3.9 (2.1-15.5) in successful patients	-
Hyun Chin Cho, et al. 2011.[9]	68 cases reported	38/68 (55.9%) overall; 17/35 (48.6%) in effective and 21/33 (63.6%) in ineffective	18.7 ±10.3 overall; 20.4 ± 10.4 in ineffective patients, and 17± 10.1 in effective patients	16±12
Juil Park, et al. 2018.[1]	0.853% [52 (45 treated)/6097]	28/52 (53.8%) overall ; 10/21 (47.6%) in effective and 10/17 (58.8%) in ineffective *	18.7±10.4 in 17 ineffective patients, and 16.8±10.4 in 21 effective patients	-

Anon Chotirosniramit, et al. 2017.[10]	3.44% [14 (1 treated)/407]	-	9.2 (0.5–26.3)	-
Ashwin Rammohan, et al. 2015.[11]	5.63% (24/426)	-	6.1 ± 5.1	-
Jihyun An, et al. 2017.[12]	1.32% (88/6663)	-	1.6 (1.0-5.3)	-
Lun-Xiu Qin, et al. 2004.[5]	0.278% (12/4324)	-	-	-
Tatsuya Orimo, et al. 2016.[2]	0.775% (6/774)	-	-	-
Yosuke Kasai, et al. 2015.[13]	1.76% (27/1538)	-	1.2 ± 0.8 (range 0.4–4.5)	-
Semi Park, et al. 2014.[8]	54 cases reported	29/54 (53.7%)	15.5±11.5 overall; 8.1±5.3 in success patients, and 23.1±10.4 in unsuccessful patients	-
Hyun Young Woo, et al. 2017.[14]	74 cases reported, 52 were previously treated	47/70 (67.1%) overall; 15/25 (60%) in favorable response patients, and 32/45 (71.1%) in poor response patients	9.58±5.80	6.1 (range 0±29 days)
Sum	1.25% (295/23632)	214/367 (58.3%) overall; 71/135 (52.6%) effective, 106/164 (64.6%) ineffective ($p<0.05$) #	-	-

* 14 patients did not undergo drainage treatment in this study.

This would also sum up to a 45.2% effectiveness rate, but these results could not be directly added to each other because not all studies adopted the same standard of effectiveness.

Supplementary Table 2. Reported rates of serum bilirubin reduction after ENBD or PTBD.

Study	2 weeks	1 month	Standard of reduction	HCC only?
R. Uberoi, et al. CVIR. 2012[18]	26.89% (224 in 833 patients)*		1-49.9% reduction	No
	41.78% (348 in 833)*		>49.9% reduction	No
Floriane Sellier, et al. Digestive and Liver Disease. 2018.[22]	64.7% (44 in 69)		50% of the pre-treatment value	No
Jongkyoung Choi, et all. J Palliat Med, 2013.[6]	65% (39 in 60)		30% reduction or to <2 mg/dL	YES
Jennifer L. Levy, et al. Abdom Radiol. 2016[20]		62% (88 patients with a pre-drainage bilirubin >5mg/dL)	≤5 mg/dL	No
		37% (106 patients with a pre-drainage bilirubin >2mg/dL)	≤2 mg/dL	No
Ankaj Khosla, et al. CVIR. 2017.[23]		38.64% (72 in 190) #	2 mg/dL.	No
Yang-Gun Suh, et al. Gut and Liver, 2014.[3]		23.8% (15 in 63)$	2mg/dL	YES
Hyun Young Woo, et al. PLoS ONE.[14]		35.7% (25/70)	3 mg/dL.	YES
Hyun Chin Cho, et al. European Journal of Gastroenterology & Hepatology 2011.[9]		51.5% (40 in 78)	30% reduction (average: preprocedural 18.7±10.3 mg/dL, with 45 (66.2%) more than 13)	YES
Juil Park, et al. Eur Radiol. 2018.[1]		55.3% (21 in 38)	30% reduction (resulting in average 7.1±6.2 mg/dL in the effective group)	YES
Semi Park, et al. Yonsei Med J 2014.[8]		42.6% (23/54)	50% reduction or to <2 mg/dL (average preprocedural: 15.5±11.5)	
Joon Woo Lee, et al. CVIR. 2002.[4]		59.1% (13 in 22)	50% of its initial value (preprocedural level <10 mg/dL in 5 patients and ≥ 10 mg/dL in 17 patients	YES

* In this study the mean time to recording of bilirubin reduction was 14 (range, 1–380) days.

Median follow-up time for last bilirubin value was 9 days (25th percentile 6 days, 75th percentile 33 days).

$ Median time interval between biliary drainage and initiation of treatment for HCC was 14 days (range, 1–43).

Supplementary Table 3. Classification of morphological features of HCC.

Feature	0	1	2	3	4	5
Tumor size	-	Maximal diameter ≤ 3cm	3cm < maximal diameter ≤ 5cm	5cm < maximal diameter ≤ 10cm	maximal diameter> 10cm or unmeasurable infiltrative lesion	-
Tumor count	-	Only one lesion visible on enhanced CT/MRI	1<Number of lesions≤3	3<Number of lesions≤10	10<Number of lesions≤20	Number of lesions >20 or unmeasurable infiltrative lesions
Abdominal lymph node metastases	-	No apparent metastases	2cm <enlarged lymph nodes ≤ 5cm	5cm <enlarged lymph nodes		
PVTT	No apparent PVTT or possible PVTT in secondary branches of the RPV or LPV	PVTT in one of the first branches of the RPV/LPV, in the RPV or LPV, or in the MPV	PVTT in two of these anatomical units (each one of the first branches of the RPV/LPV or the RPV, LPV and the MPV was considered a unit)	PVTT in 3 – 5 units but not diffusely occluding all portal vein branches in the right or left lobe	All portal vein branches in the right or left lobe were occluded	All portal vein branches in both the right and left lobe were occluded

Ueda classification of the bile duct involvement	-	Secondary branch of the biliary tree was affected	First branches of the biliary tree	The common hepatic or biliary duct was affected	-	-
Bismuth's classification of the bile duct involvement	-	Limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts	Involves the confluence of the right and left hepatic ducts	Type II and extends to the bifurcation of the right/left hepatic duct	Extending to the bifurcations of both right and left hepatic ducts or multifocal involvement.	At the junction of common bile duct and cystic duct

CT: computed tomography; LPV: left portal vein; MPV: main portal vein; MRI: magnetic resonance imaging; PVTT: portal vein tumor thrombosis; RPV: right portal vein.

3. Methods

3.1. Patients

This retrospective study conformed to the ethical principles enshrined in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the institutional review board of the Third Affiliated Hospital of Sun Yat-sen University. The requirement for informed consent was waived off. We searched for HCC patients who underwent PTBD for obstructive jaundice between January 1, 2010 and December 31, 2018 in the databases of the Third Affiliated Hospital of Sun Yat-sen University, the First Affiliated Hospital of Sun Yat-sen University, the Fifth Affiliated Hospital of Sun Yat-sen University and Maoming People's Hospital.

The inclusion criteria were: (1) diagnosis of HCC based on histologic or non-invasive criteria defined by major clinical guidelines with a history of HBV infection-related cirrhosis [15,16]. (2) serum total bilirubin level >3 mg/dL within 3 days prior to the PTBD procedure; (3) typical signs of biliary tract obstruction in computed tomography (CT), magnetic resonance imaging (MRI), or percutaneous transhepatic cholangiography images; and (4) indication for PTBD: to relieve obstructive jaundice [1,9,12,14]. The exclusion criteria were: (1) improperly drained patients, defined as less than 75% (determined by at least two interventional radiologists upon review of the cholangiogram, preprocedural and follow-up imaging) of remaining liver segments drained [15,19] or performance of a secondary drainage-related procedure after the first week post-primary PTBD procedure; (3) death within the first post-procedural week or lost to follow-up after discharge; and (4) history of excessive alcohol consumption, Hep C infection, or nonalcoholic steatohepatitis.

3.2. Procedures

Routine pre-PTBD blood indices were obtained from all four participating hospitals. Preprocedural CT/MRI images were reviewed by at least 2 radiologists, and morphological features of the HCC were determined (Supplementary table 3). The interval between clinical onset of jaundice and PTBD was recorded as time-to-treatment (in days), as previously reported (Supplementary Table 1) [1,5,10,12].

PTBD procedures were performed by interventional radiologists using standard techniques [1,6]. The right or left approach was determined based on the location and the extent of the bile duct obstruction by the tumor as well as the feasibility of each approach.

3.3. Outcome

Follow-up medical records were reviewed. Morbidity, mortality, and laboratory data within a month after PTBD were recorded. Effective drainage was defined separately for calculation of the respective nomogram as: 1) any decrease in TBil level; 2) TBil lowered to <5 mg/dL; 3) 3 mg/dL; or 4) 2 mg/dL. Follow up test results obtained 4 weeks after the PTBD procedure were evaluated, [1,4,8,9,12,14] and the lowest TBil level before death or before succeeding tests showed a steady increase in TBil were recorded and compared with the efficacy standards. The first follow up TBil test result that was lower than 2 mg/dL was recorded as the lowest post-procedural TBil.

3.4. Statistical Analysis

Statistical analysis was conducted with R software (version 3.5.1; http://www.Rproject.org). Two-sided *P* values < 0.05 were considered indicative of statistical significance. The least absolute shrinkage and selection operator (LASSO) method, which has been reported to be suitable for the regression of high-dimensional data, was used to select the most useful predictive characteristics from the data set [25]. Multivariable logistic regression analysis was then started and the variables that survived the LASSO model according to the 1-standard error selection criterion were further tested by backward stepwise selection using the likelihood ratio test with Akaike's information criterion as the stopping rule. Calibration curves were plotted to assess the accuracy of the predictive function, accompanied with the Hosmer-Lemeshow test. Discrimination performance of the prediction model was assessed using Area Under Curve of Receiver Operating Characteristic Curve (ROC). Decision curve analysis (DCA) was conducted to determine the practicality of the prediction model by quantifying the probability of net benefits at different thresholds [27]. We also performed univariate analysis on the baseline data. Continuous variables and categorical grades were presented

as mean ± standard deviation; dichotomous variables were expressed as frequencies and compared using the Chi-squared test or the Fisher exact test. P value < 0.05 was considered indicative of statistical significance. A commercially available software package (SPSS 19.0 for Windows) was used for univariate analyses.

4. Results

4.1. Demographics and Univariate Analysis

The final population included for analysis consisted of 138 patients (Supplementary Figure 1). The effective rate was 73.19% (101 in 138 patients) when determined by any decrease of TBil 4 weeks after PTBD; 47.10% when determined by lowest recorded post-procedural TBil <5 mg/dL (65 in 138 patients or 44.70%, 59 in 132 patients whose preprocedural TBil levels were >5 mg/dL). The effective rate was 41.30% when the standard was 3 mg/dL (57 in 138 patients), and 31.88% when the standard was 2 mg/dL (44 in 138 patients). Among the included patients, 6 had pre-PTBD Tbil levels <5 mg/dL; they all showed lowest postprocedural Tbil levels of <3 mg/dL while two of them did not reach the 2 mg/dL standard. Three patients died on the 10th, 12th, and 17th day, respectively. The cause of death included multiple organ failure in two patients and variceal hemorrhage in one patient. The mean period to achieve the lowest level of TBil by patients in the 5mg/dL, 3mg/dL, and 2mg/dL groups was 66.2±39.5 days. The clinical characteristics of patients and the results of univariate analysis are summarized in **Table 1**.

Supplementary Figure 1. Patient flow diagram.

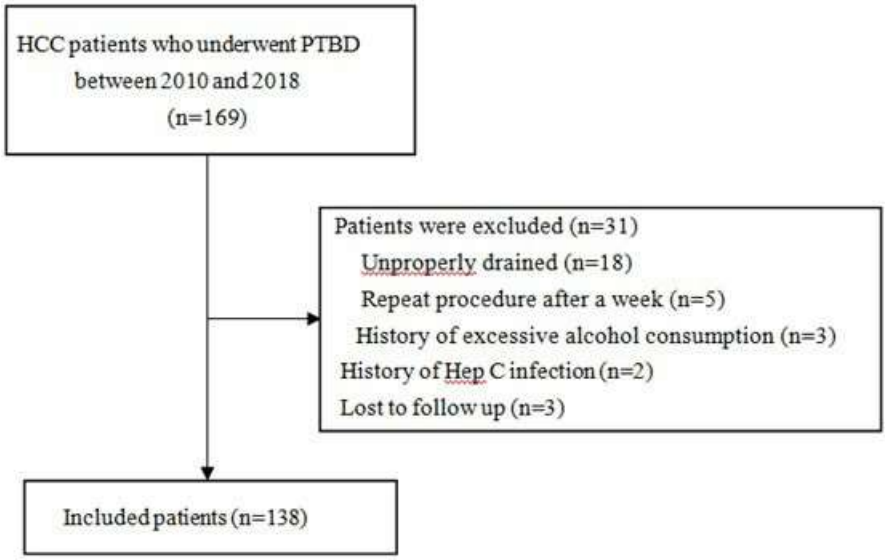


Table 1: Clinical and laboratory characteristics of the patients.

Characteristic	Overall	Ineffective drainage	Effective drainage	*P* value
Number of patients	138	37 (26.81%, no decrease)	101 (73.19, any decrease)	N/A
		73 (52.90%, >5mg/dL)	65 (47.10%, <5mg/dL)	N/A
		81 (58.70%, >3mg/dL)	57 (41.30%, <3mg/dL)	N/A
		94 (68.12%, >2mg/dL)	44 (31.88%, <2mg/dL)	N/A
Gender (Female)	21 (15.2%)	5 (13.5%, no decrease)	16 (15.8%, any decrease)	0.484
		10 (13.7%, >5mg/dL)	11 (16.9%, <5mg/dL)	0.599
		11 (13.6%, >3mg/dL)	10 (17.5%, <3mg/dL)	0.523
		13 (13.8%, >2mg/dL)	8(18.2%, <2mg/dL)	0.507
Age, mean±SD, years	51.7±11.0	52.9±9.8 (no decrease)	51.2±11.5(any decrease)	0.427
		52.2±10.4 (>5mg/dL)	51.1±11.6 (<5mg/dL)	0.577
		52.4±10.4 (>3mg/dL)	50.6±11.7 (<3mg/dL)	0.359
		52.7±10.4 (>2mg/dL)	49.5±12.0 (<2mg/dL)	0.12

Previous antitumor treatment	91 (65.9%)	26 (70.3%, no decrease)	65 (64.4%, any decrease)	0.331
		48 (65.8%, >5mg/dL)	43 (66.2%, <5mg/dL)	0.96
		54 (66.7%, >3mg/dL)	37 (64.9%, <3mg/dL)	0.83
		64 (68.1%, >2mg/dL)	27 (61.4%, <2mg/dL)	0.437
Interval between HCC diagnosis and PTBD, mean±SD, months	17.2±23.5	12.9±14.2 (no decrease)	18.8±25.8 (any decrease)	0.194
		14.2±17.5 (>5mg/dL)	20.7±28.2 (<5mg/dL)	0.104
		14.7±20.5 (>3mg/dL)	20.9±26.5 (<3mg/dL)	0.126
		14.5±19.8 (>2mg/dL)	22.9±28.8 (<2mg/dL)	0.049*
Time to PTBD#, mean±SD, days	22.8±15.8	27.2±19.2 (no decrease)	21.2±13.9 (any decrease)	0.046*
		24.5±15.7 (>5mg/dL)	20.8±15.6 (<5mg/dL)	0.172
		23.9±15.3 (>3mg/dL)	21.2±16.3 (<3mg/dL)	0.34
		23.7±15.3 (>2mg/dL)	20.8±16.6 (<2mg/dL)	0.314
Preprocedural serum total bilirubin level, mean±SD, μmol/L	285.1±155.5	339.2±141.3 (no decrease)	265.3±154.9 (any decrease)	0.013*
		329.0±149.6 (>5mg/dL)	235.9±145.7 (<5mg/dL)	0.0004*
		325.9±151.8 (>3mg/dL)	227.2±140.1(<3mg/dL)	0.0002*
		308.4±153.1 (>2mg/dL)	235.3±146.7(<2mg/dL)	0.009*
Direct bilirubin level, mean±SD, μmol/L	210.3±111.4	239.5±102.8 (no decrease)	199.6±113.0 (any decrease)	0.013*
		238.4±106.2 (>5mg/dL)	178.9±107.7 (<5mg/dL)	0.002*
		237.1±108.2 (>3mg/dL)	172.2±103.5 (<3mg/dL)	0.0006*
		226.0±108.9 (>2mg/dL)	176.9±107.9 (<2mg/dL)	0.015*
Indirect bilirubin level, mean±SD, μmol/L	74.8±53.0	99.6±49.9 (no decrease)	65.7±50.9 (any decrease)	0.0007*
		90.6±55.6 (>5mg/dL)	57.0±43.1 (<5mg/dL)	0.0002*
		88.7±55.1 (>3mg/dL)	55.0±42.1 (<3mg/dL)	0.0002*
		82.4±54.7 (>2mg/dL)	58.4±44.2 (<2mg/dL)	0.013*
Indirect bilirubin/direct bilirubin ratio, mean±SD	0.35±0.16	0.42±0.15 (no decrease)	0.33±0.15 (any decrease)	0.001*
		0.38±0.17 (>5mg/dL)	0.32±0.14 (<5mg/dL)	0.010*
		0.38±0.16 (>3mg/dL)	0.31±0.14 (<3mg/dL)	0.019*
		0.36±0.16 (>2mg/dL)	0.32±0.14 (<2mg/dL)	0.157
Albumin, mean±SD, g/L	33.7±4.2	33.1±3.6 (no decrease)	33.9±4.4 (any decrease)	0.296
		32.8±3.8 (>5mg/dL)	34.8±4.4 (<5mg/dL)	0.005*
		32.8±3.7 (>3mg/dL)	35.0±4.6 (<3mg/dL)	0.003*
		33.0±3.8 (>2mg/dL)	35.1±4.6 (<2mg/dL)	0.005*

INR, mean±SD	1.13±0.21	1.22±0.26 (no decrease)	1.11±0.17 (any decrease)	0.003*
		1.21±0.23 (>5mg/dL)	1.05±0.14 (<5mg/dL)	<0.001*
		1.20±0.22 (>3mg/dL)	1.05±0.14 (<3mg/dL)	<0.001*
		1.18±0.22 (>2mg/dL)	1.04±0.13 (<2mg/dL)	0.0001*
Ascites, n (%)	131 (94.9%)	36 (97.3%, no decrease)	95 (94.1%, any decrease)	0.443
		69 (94.5%, >5mg/dL)	62 (95.4%, <5mg/dL)	0.817
		77 (95.1%, >3mg/dL)	54 (94.7%, <2mg/dL)	0.931
		89 (94.7%, >2mg/dL)	42 (95.5%, <2mg/dL)	847
Creatinine, mean±SD, μmol/L	66.4±17.1	68.1±19.4 (no decrease)	65.8±16.0 (any decrease)	0.497
		65.9±16.5 (>5mg/dL)	67.0±17.6 (<5mg/dL)	0.705
		65.2±16.0 (>3mg/dL)	68.1±18.3 (<3mg/dL)	0.329
		65.5±16.6 (>2mg/dL)	68.5±17.8 (<2mg/dL)	0.333
[Na+] level, mean±SD, mmol/L	136.1±4.1	134.2±4.6 (no decrease)	136.8±3.7 (any decrease)	0.0008*
		135.2±4.2 (>5mg/dL)	137.1±3.8 (<5mg/dL)	0.007*
		135.4±4.1 (>3mg/dL)	137.1±1.2 (<3mg/dL)	0.017*
		135.6±3.9 (>2mg/dL)	137.2±4.3 (<2mg/dL)	0.036
MELD, mean±SD	18.5±4.7	21.1±4.2 (no decrease)	17.5±4.4 (any decrease)	<0.001*
		20.3±4.0 (>5mg/dL)	16.4±4.5 (<5mg/dL)	<0.001*
		20.0±4.0 (>3mg/dL)	16.3±4.7 (<3mg/dL)	<0.001*
		19.5±4.2 (>2mg/dL)	16.3±4.8 (<2mg/dL)	0.0002*
Child-Pugh score, mean±SD	7.8±1.4	8.5±1.5 (no decrease)	7.6±1.3 (any decrease)	0.0009*
		8.3±1.4 (>5mg/dL)	7.3±1.2 (<5mg/dL)	<0.001*
		8.2±1.4 (>3mg/dL)	7.2±1.2 (<3mg/dL)	<0.001*
		8.1±1.4 (>2mg/dL)	7.2±1.1 (<2mg/dL)	0.0001*
Cholinesterase, mean±SD, U/L	3444.4±1607.5	2973.1±1451.2 (no decrease)	3617.0±1619.3 (any decrease)	0.036*
		3004.2±1308.6 (>5mg/dL)	3938.6±1749.5 (<5mg/dL)	
		3007.7±1289.9 (>3mg/dL)	4064.9±1786.0 (<3mg/dL)	0.0005*
		3035.1±1289.4 (>2mg/dL)	4318.5±1836.3 (<2mg/dL)	0.0001*
				<0.001*
GGT, mean±SD, U/L	449.2±373.3	353.6±260.4 (no decrease)	484.2±399.5 (any decrease)	0.068
		345.8±234.5 (>5mg/dL)	565.3±454.4 (<5mg/dL)	0.0005*
		394.6±311.2 (>3mg/dL)	526.8±432.4 (<3mg/dL)	0.040*
		458.0±394.0 (>2mg/dL)	430.4±319.0 (<2mg/dL)	0.688

ALP, mean±SD, U/L	394.3±265.3	316.8±204.7 (no decrease)	422.7±277.6 (any decrease)	0.037*
		340.0±216.7 (>5mg/dL)	455.3±297.6 (<5mg/dL)	0.010*
		389.1±291.8 (>3mg/dL)	401.8±219.1 (<3mg/dL)	0.783
		400.5±282.2 (>2mg/dL)	381.1±220.6 (<2mg/dL)	0.691
Pre-albumin, mean±SD, mg/L	66.7±33.2	58.1±29.9 (no decrease)	69.8±33.7 (any decrease)	0.067
		57.0±28.1 (>5mg/dL)	77.5±34.9 (<5mg/dL)	0.0002*
		57.6±27.6 (>3mg/dL)	79.5±35.9 (<3mg/dL)	<0.001*
		58.5±27.8 (>2mg/dL)	84.1±36.6 (<2mg/dL)	<0.001*
AFP, mean±SD, ng/ml	1427.4±3469.6	1150.9±2073.4 (no decrease)	1528.7±3860.8 (any decrease)	0.306
		2471.4±14020.8 (>5mg/dL)	1947±4563.2 (<5mg/dL)	
				0.776
		2251.2±13327.6 (>3mg/dL)	2186.6±4919.8 (<3mg/dL)	0.972
		2375.5±12504.4 (>2mg/dL)	1902.0±4915.1 (<2mg/dL)	0.81
HBV-DNA, mean±SD	1.14E+06±6.42E+06	1.93E+06±7.50 E+06 (no decrease)	8.46E+05±6.00E+06 (any decrease)	0.573
		1.04E+06±5.35 E+06 (>5mg/dL)	1.25E+06±7.41 E+06 (<5mg/dL)	0.848
		9.39E+05±5.09 E+06 (>3mg/dL)	1.42E+06±7.89 E+06 (<3mg/dL)	0.667
		1.44E+06±7.63 E+06 (>2mg/dL)	4.87E+05±1.93E+06 (<2mg/dL)	0.418
Preprocedural cholangitis, n (%)	31 (22.5%)	12 (32.4%, no decrease)	19 (18.8%, any decrease)	0.382
		20 (27.4%, >5mg/dL)	11 (16.9%, <5mg/dL)	0.141
		23 (28.4%, >3mg/dL)	8 (14.0%, <3mg/dL)	0.047*
		23 (24.5%, >2mg/dL)	8 (18.2%, <2mg/dL)	0.41
WBC, mean±SD, 10^9/L	7.7±3.7	6.8±2.9 (no decrease)	7.9±3.9 (any decrease)	0.123
		7.6±3.8 (>5mg/dL)	7.7±3.5 (<5mg/dL)	0.855
		7.5±3.7 (>3mg/dL)	7.9±3.7 (<3mg/dL)	0.568
		7.5±3.5 (>2mg/dL)	8.1±3.9 (<2mg/dL)	0.355
Hemoglobin level, mean±SD, g/L	117.0±24.8	117.7±18.6 (no decrease)	116.7±26.6 (any decrease)	0.832
		115.3±18.5 (>5mg/dL)	118.8±30.2 (<5mg/dL)	0.409
		113.8±18.6 (>3mg/dL)	121.5±30.9 (<3mg/dL)	0.074
		115.3±19.1 (>2mg/dL)	120.5±33.6 (<2mg/dL)	0.255
Platelet, mean±SD, 10^9/L	203.5±96.5	139.8±73.3 (no decrease)	226.8±92.9 (any decrease)	<0.001*
		169.1±77.7 (>5mg/dL)	242.1±100.1 (<5mg/dL)	<0.001*
		176.0±81.4 (>3mg/dL)	242.6±101.7 (<3mg/dL)	<0.001*
		183.8±88.2 (>2mg/dL)	245.6±98.7 (<2mg/dL)	0.0004
Monocyte, mean±SD, 10^9/L	0.082±0.028	0.66±0.36 (no decrease)	0.57±0.32 (any decrease)	0.158
		0.62±0.34 (>5mg/dL)	0.65±0.37 (<5mg/dL)	0.625
		0.60±0.33 (>3mg/dL)	0.68±0.38 (<3mg/dL)	0.212
		0.59±0.32 (>2mg/dL)	0.72±0.41 (<2mg/dL)	0.047*

Neutrophil, mean±SD, 10^9/L	5.7±3.2	4.9±2.1 (no decrease)	5.9±3.5 (any decrease)	0.096
		5.6±3.3 (>5mg/dL)	5.7±3.1 (<5mg/dL)	0.928
		5.6±3.2 (>3mg/dL)	5.8±3.2 (<3mg/dL)	0.75
		5.5±3.0 (>2mg/dL)	6.0±3.5 (<2mg/dL)	0.442
Lymphocyte, mean±SD, 10^9/L	1.1±0.54	1.0±0.62 (no decrease)	1.1±0.50 (any decrease)	0.352
		1.1±0.55 (>5mg/dL)	1.2±0.51 (<5mg/dL)	0.264
		1.0±0.52 (>3mg/dL)	1.2±0.54 (<3mg/dL)	0.123
		1.1±0.53 (>2mg/dL)	1.2±0.53 (<2mg/dL)	0.321
Neutrophil/Lymphocyte ratio, mean±SD	6.9±8.2	6.1±3.7 (no decrease)	7.2±9.3 (any decrease)	0.467
		7.1±7.5 (>5mg/dL)	6.6±8.9 (<5mg/dL)	0.737
		7.0±7.1 (>3mg/dL)	6.8±9.5 (<3mg/dL)	0.924
		6.6±6.7 (>2mg/dL)	7.5±10.7 (<2mg/dL)	0.539
Tumor size, mean±SD	2.82±0.97	2.81±1.04 (no decrease)	2.82±0.94 (any decrease)	0. 953
		2.79±1.02 (>5mg/dL)	2.85±0.90 (<5mg/dL)	0.756
		2.81±1.02 (>3mg/dL)	2.82±0.88 (<3mg/dL)	0.954
		2.81±0.97 (>2mg/dL)	2.84±0.95 (<2mg/dL)	0.855
Tumor count, mean±SD	2.57±1.16	2.81±1.04 (no decrease)	2.49±1.13 (any decrease)	0.146
		2.76±1.13 (>5mg/dL)	2.35±1.16 (<5mg/dL)	0.037*
		2.77±1.11 (>3mg/dL)	2.30±1.17 (<3mg/dL)	0.020*
		2.77±1.11 (>2mg/dL)	2.16±1.15 (<2mg/dL)	0.004*
Tumor taking up more than half of total liver volume, n (%)	5 (3.6%)	3 (8.1%, no decrease)	2 (2.0%, any decrease)	0.088
		4 (5.5%, >5mg/dL)	1(1.5%, <5mg/dL)	0.216
		4 (4.9%, >3mg/dL)	1 (1.8%, <3mg/dL)	0.324
		4 (4.3%, >2mg/dL)	1 (2.3%, <2mg/dL)	0.561
Lymph node	1.32±0.62	1.35±0.67 (no decrease)	1.31±0.60 (any decrease)	0.709
		1.37±0.67 (>5mg/dL)	1.26±0.53 (<5mg/dL)	0.304
		1.38±0.70 (>3mg/dL)	1.23±0.46 (<3mg/dL)	0.147
		1.35±0.66 (>2mg/dL)	1.25±0.48 (<2mg/dL)	0.371
Bismuth classification, mean±SD	3.41±0.79	3.57±0.72 (no decrease)	3.35±0.80 (any decrease)	0.709
		3.51±0.74 (>5mg/dL)	3.28±0.87 (<5mg/dL)	0.098
		3.49±0.74 (>3mg/dL)	3.26±0.89 (<3mg/dL)	0.102
		3.45±0.78 (>2mg/dL)	3.30±0.87 (<2mg/dL)	0.311
Bismuth Class IV, n (%)	77 (55.8)	25 (67.6%, no decrease)	52 (51.5%, any decrease)	0.064
		45 (61.6%, >5mg/dL)	32 (36.3%, <5mg/dL)	0.143
		49 (60.5%, >3mg/dL)	28 (49.1%, <3mg/dL)	0.185
		55 (58.5%, >2mg/dL)	22 (50.0%, <2mg/dL)	0.348
Ueda classification, mean±SD	2.88±0.44	2.92±0.36 (no decrease)	2.86±0.47 (any decrease)	0.501
		2.95±0.28 (>5mg/dL)	2.80±0.56 (<5mg/dL)	0.054

		2.93±0.34 (>3mg/dL)	2.81±0.54 (<3mg/dL)	0.121
		2.93±0.33 (>2mg/dL)	2.77±0.60 (<2mg/dL)	0.059
Ueda classification Class III, n (%)	127 (92.0%)	35 (94.6%, no decrease)	92 (91.1%, any decrease)	0.501
		70 (95.9%, >5mg/dL)	57 (87.7%, <5mg/dL)	0.076
		77 (95.1%, >3mg/dL)	50 (87.7%, <3mg/dL)	0.117
		89 (94.7%, >2mg/dL)	38 (86.4%, <2mg/dL)	0.093
Hepatic vein tumor thrombosis, n (%)	49 (35.5%)	18 (48.6%, no decrease)	31 (30.7%, any decrease)	0.051
		34 (46.6%, >5mg/dL)	15 (23.1%, <5mg/dL)	0.004*
		37 (45.7%, >3mg/dL)	12 (26.7%, <3mg/dL)	0.003*
		39 (41.5%, >2mg/dL)	10 (22.7%, <2mg/dL)	0.032*
PVT classification, mean±SD	1.73±1.53	2.35±1.56 (no decrease)	1.50±1.45 (any decrease)	0.004*
		2.22±1.42 (>5mg/dL)	1.18±1.46 (<5mg/dL)	<0.001*
		2.12±1.44 (>3mg/dL)	1.18±1.46 (<3mg/dL)	0.0002*
		1.99±1.50 (>2mg/dL)	1.18±1.43 (<2mg/dL)	0.004*
PVT classification ≥4, n (%)	24 (17.4%)	13 (35.1%, no decrease)	11 (10.9%, any decrease)	0.0009*
		17 (23.3%, >5mg/dL)	7 (10.8%, <5mg/dL)	0.053
		17 (21.0%, >3mg/dL)	7 (12.3%, <3mg/dL)	0.184
		19 (20.2%, >2mg/dL)	5 (11.4%, <2mg/dL)	0.201
PVT classification ≥3, n (%)	48 (34.8%)	18 (48.6%, no decrease)	30 (29.7%, any decrease)	0.038*
		33 (45.2%, >5mg/dL)	15 (23.1%, <5mg/dL)	0.006*
		36 (44.4%, >3mg/dL)	12 (21.1%, <3mg/dL)	0.005*
		39 (41.5%, >2mg/dL)	9 (20.5%, <2mg/dL)	0.016*
Number of catheters used, mean±SD £	1.52±0.70	1.43±0.59 (no decrease)	1.55±0.72 (any decrease)	0.364
		1.53±0.68 (>5mg/dL)	1.51±0.70 (<5mg/dL)	0.824
		1.56±0.68 (>3mg/dL)	1.47±0.70 (<3mg/dL)	0.498
		1.53±0.68 (>2mg/dL)	1.50±0.72 (<2mg/dL)	0.803
More than 1 catheter used, n (%)	58 (42.0%)	14 (43.6%, no decrease)	44 (10.9%, any decrease)	0.546
		32 (43.8%, >5mg/dL)	26 (40.0%, <5mg/dL)	
				0.649
		37 (45.7%, >3mg/dL)	21 (36.8%, <3mg/dL)	0.3
		41 (43.6%, >2mg/dL)	17 (38.6%, <2mg/dL)	0.581
One suspected undrained segment, n (%)	45 (32.6%)	18 (48.6%, no decrease)	27 (26.7%, any decrease)	0.014*
		30 (41.1%, >5mg/dL)	15 (23.1%, <5mg/dL)	
		31 (38.3%, >3mg/dL)	14 (24.6%, <3mg/dL)	0.024*
				0.091
		35 (37.2%, >2mg/dL)	10 (22.7%, <2mg/dL)	0.09

Effectiveness was determined according to whether post-PTBD serum level of total bilirubin showed any decrease compared to preprocedural level, or whether the lowest post-PTBD serum level of total bilirubin was <5 mg/dL, 3 mg/dL, or 2 mg/dL. For conciseness, these are denoted as 'any decrease', '<5mg/dL', '<3mg/dL', '<2mg/dL' or 'no decrease', '>5mg/dL', '>3mg/dL', and '>2mg/dL' in this table.

AFP: α-fetoprotein; ALP: alkaline phosphatase; GGT: serum γ-glutamyl transpeptidase; HCC: hepatocellular carcinoma; INR: international normalized ratio; MELD: Model for End-stage Liver Disease; PTBD: percutaneous transhepatic biliary drainage; PVT: portal vein thrombosis; SD: standard deviation; WBC: white blood cell count.

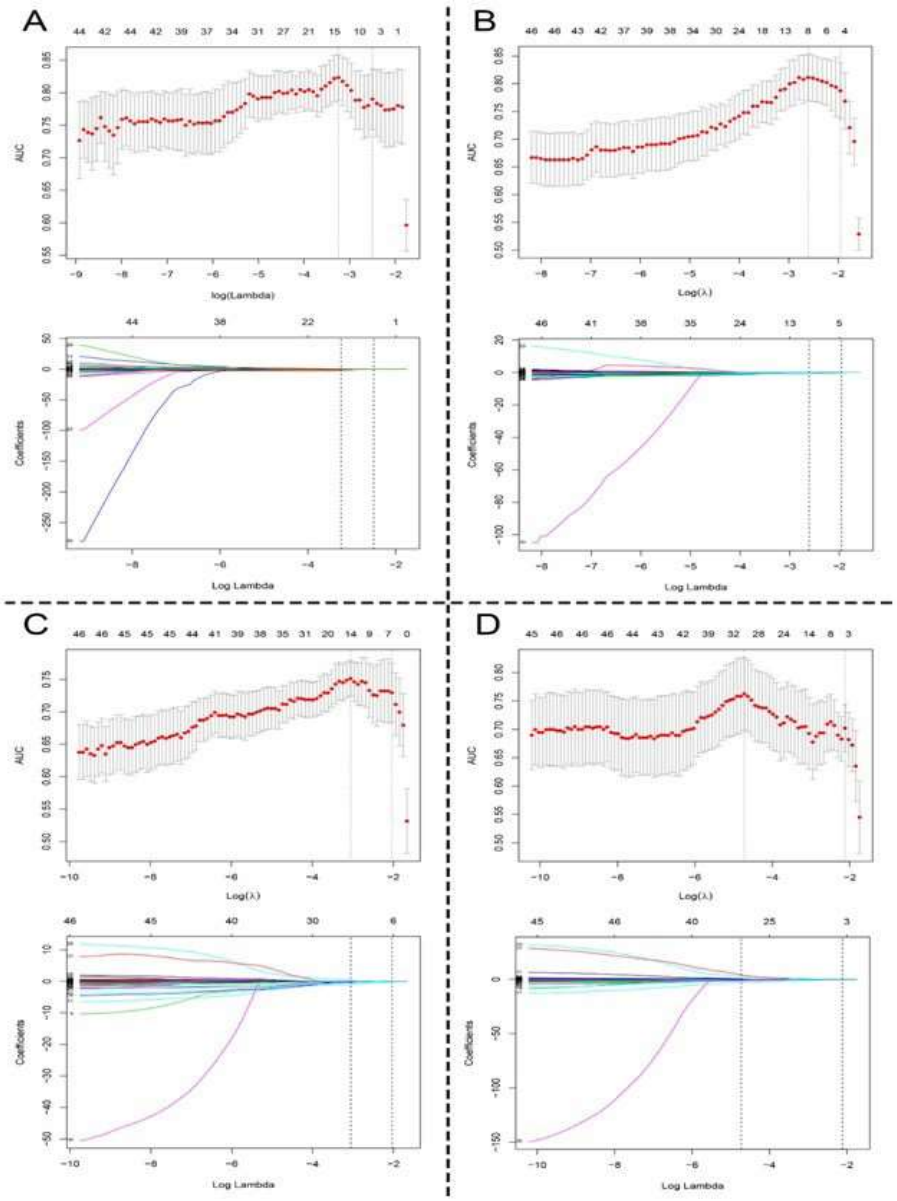
* $P<0.05$

The variable "time to treatment" represents the interval between clinical onset of jaundice and PTBD procedure counted in days.

£: Differences in drainage type (internal, external or both) showed no significance between the two groups.

4.2. Feature Selection

Based on the feature data of the 138 patients in our cohort that had non-zero coefficients in the LASSO logistic regression model, 46 features were reduced to 5 potential predictors when looking at any decrease, to 4 potential predictors when the endpoint was set at <5 mg/dL, to 6 potential predictors for endpoint of 3 mg/dL, and to 5 potential predictors for endpoint of 2 mg/dL (Supplementary Figure 2). The indirect bilirubin/direct bilirubin ratio, time-to-treatment, Model for End-stage Liver Disease (MELD) score, platelet count, and portal vein thrombosis (PVT) were selected as potential risk factors for any decrease in TBil. International normalized ratio (INR), MELD score, platelet count, and PVT were selected as potential risk factors for a decrease in TBil to <5 mg/dL. INR, Child-Pugh score, MELD score, cholinesterase level (CHE), platelet count, and PVT were selected as potential risk factors for a decrease to 3 mg/dL, while INR, MELD score, CHE, prealbumin level, and platelet count were selected as potential risk factors for a decrease to 2 mg/dL.



Supplementary Figure 2. Supplementary figure 2A through 2D represented variable selection for prediction of effectiveness using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model for the any decrease, 5mg/dL, 3mg/dL, and 2mg/dL endpoints respectively. In figure 2A for example, upper panel showed tuning parameter lambda selection using 10-fold cross-validation via minimum criteria (see the left dotted vertical line) and the 1 standard error of the minimum criteria (the 1-SE criteria, see the right dotted line). The value of area under the receiver operating characteristic (AUC) curve was plotted versus log (lambda). The number displayed on the top represents the number of leftover variables in each of the corresponding lambda. The lower panel showed coefficient profiles of the studied variables. A coefficient profile plot was generated against the log (lambda) sequence. Vertical lines were drawn at the value selected using 10-fold cross-validation based on the minimum criteria (see the left dotted vertical line) and the 1-SE criteria (see the right dotted line). Here in the any decrease model, 1-SE criterion was selected as optimal, thus resulting in 5 ultimate variables with nonzero coefficients for effectiveness. In the 5 mg/dL (2B) model, 4 ultimate variables with nonzero coefficients for effectiveness were selected, in the 3mg/dL (2C) model, 6 variables were selected and in the 2mg/dL (2D) model, 5 were selected.

4.3. Development of a Prediction Model

Multivariable logistic regression analysis was started with the potential predictors. During the backward step-wise selection process, indirect bilirubin/direct bilirubin ratio was eliminated from the model for any decrease in TBil, and the remaining four predictors, i.e., time to treatment (β value, -0.0475), MELD score (β value, -0.1212), platelet count (β value, 0.0122), and PVT (β value, -0.5382) were retained as the predictors. Using the same process, INR and Child-Pugh scores were eliminated, and the remaining four predictors, i.e., MELD score (β value, -0.1587), CHE (β value, 0.0003), platelet count (β value, 0.0063), and PVT (β value, -0.4306) were retained as the predictors in the model for a decrease in TBil to 3 mg/dL. INR was eliminated and CHE (β value, 0.0003), MELD score (β value, -0.1011), platelet count (β value, 0.0051), and prealbumin level (β value, 0.0118) were retained as predictors in the model for a decrease in TBil to 2 mg/dL. INR (β value, -2.6247), MELD score (β value, -0.1507), platelet count (β value, 0.0082), and PVT (β value, -0.4896) were retained as predictors in the model for a decrease in TBil to <5 mg/dL. Models were presented as nomograms (Table 2, Figure 1).

Table 2: Independent Predictors Included in the 4 Nomograms for Effective PTBD in HCC Patients with Obstructive Jaundice.

Endpoints	Variable	Coef (βvalue)	*P* value
Any decrease	Time_to_treatment	-0.0475	0.0015
	MELD	-0.1212	0.0235
	Platelet count	0.0122	0.0004
	PVT	-0.5382	0.0019
5mg/dL	INR	-2.6247	0.0831
	MELD	-0.1507	0.0122
	Platelet count	0.0082	0.0014
	PVT	-0.4896	0.0012
3mg/dL	MELD	-0.1587	0.0023
	CHE	0.0003	0.0331
	Platelet count	0.0063	0.0078
	PVT	-0.4306	0.0033
2mg/dL	CHE	0.0003	0.0755
	MELD	-0.1011	0.0474
	Platelet count	0.0051	0.0253
	Prealbumin level	0.0118	0.1332

CHE: cholinesterase level; HCC: hepatocellular carcinoma; INR: international normalized ratio; MELD: Model for End-stage Liver Disease; PTBD: percutaneous transhepatic biliary drainage; PVT: portal vein thrombosis.

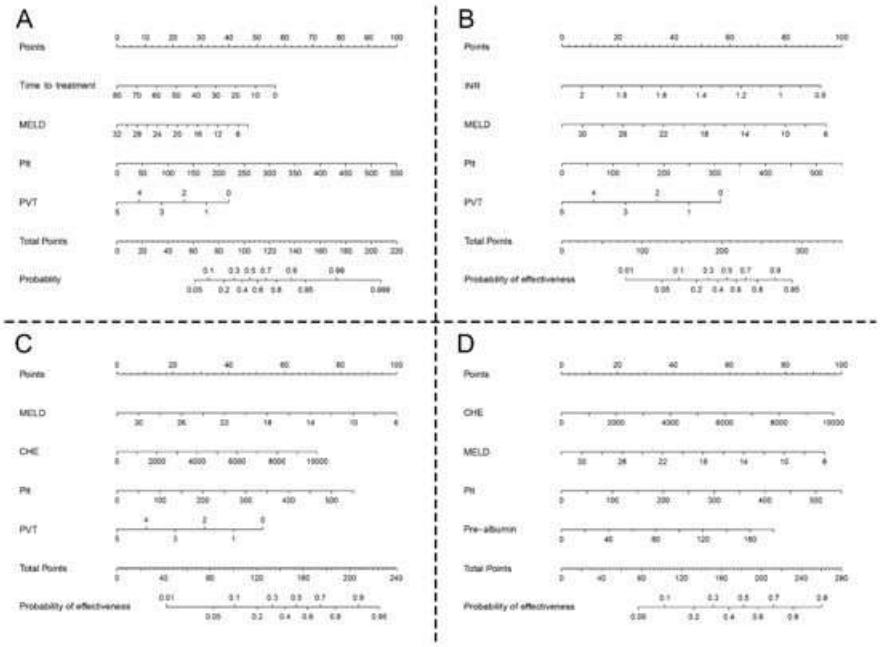


Figure 1: Nomograms for predicting the effectiveness of percutaneous transhepatic biliary drainage.

The incorporated variables for the nomograms predicting any decrease, decrease to a lowest level of 5 mg/dL, decrease to 3 mg/dL, and to 2 mg/dL are shown in figures 1A to 1D, respectively, with four variables ultimately selected in each model.

4.4. Apparent Performance and Internal Validation of the Nomogram

We used data of the same group of patients as the internal validation data set. The calibration curves of the nomograms for the effectiveness (judged by different standards) of PTBD demonstrated good agreement between prediction and observation in our cohort (Figure 2). The Hosmer-Lemeshow test yielded nonsignificant statistics (P = 0.891 for any decrease model, 0.634 for <5 mg/dL, P=0.956 for 3 mg/dL, and 0.977 for 2 mg/dL), which suggested that there was little departure from perfect fit. The C-index for the prediction nomogram for any decrease in TBil was 0.847 [95% confidence interval (CI), 0.775–0.919]. The C-index for <5 mg/dL, 3 mg/dL, and 2 mg/dL endpoints were 0.843 (95% CI, 0.777–0.909), 0.818 (95% CI, 746–0.890), and 0.776 (95% CI, 0.691–0.861), respectively (Figure 2). On ROC curve analysis, the optimal cut-off values were 0.786 for any decrease in TBil, 0.554 for <5 mg/dL, 0.557 for 3 mg/dL, and 0.301 for 2 mg/dL (Supplementary Figure 3).

4.5. Clinical Use

The DCA graphs for the nomogram are presented in Figure 3. The decision curves showed that should the threshold probability be >20% and <95% (implying that if a patient or doctor is willing to undergo/perform PTBD if any prediction model showed >20% and <95% chance of any decrease), use of the nomogram to predict effectiveness would benefit the patient more compared to that with either the treat-all-patients scheme or the treat-none scheme. The threshold pairs were 20% and 90% for <5 mg/dL, 20% and 95% for 3 mg/dL, and 20% and 85% for 2 mg/dL, respectively.

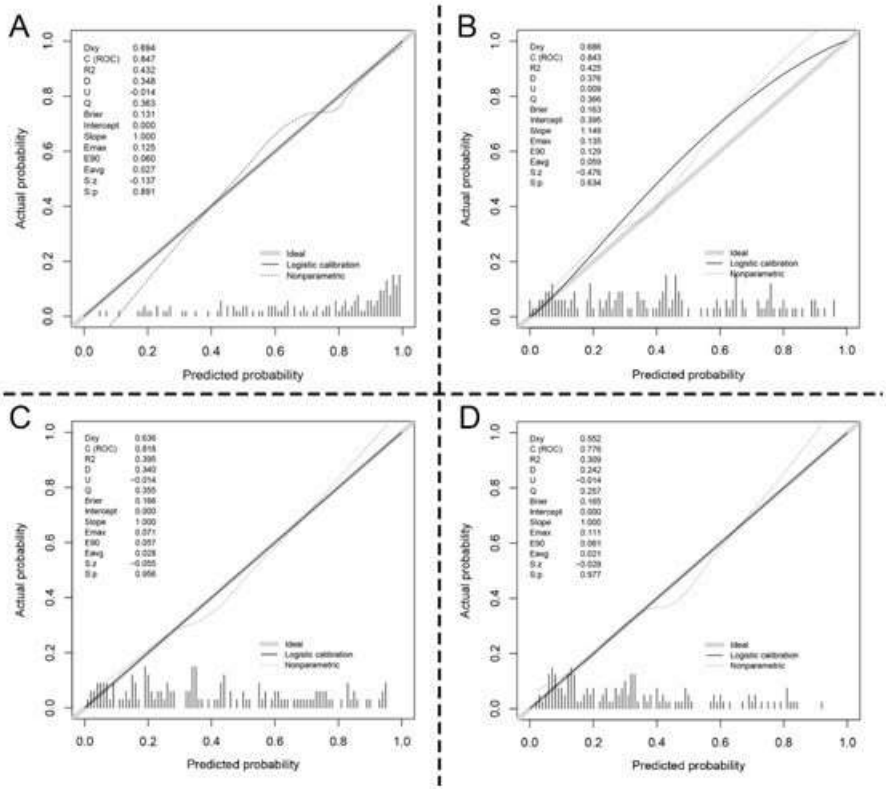


Figure 2. Calibration curves of the developed nomograms for effectiveness.

Figure 2 Calibration curves of the prediction models for any decrease, decrease to a lowest level of 5 mg/dL, decrease to 3 mg/dL, and to 2 mg/dL were not significantly deviated from the diagonal (ideal) lines. *P* values > 0.05 shown in figures 2A to 2D indicate that the predicted probabilities of the nomograms were relatively accurate.

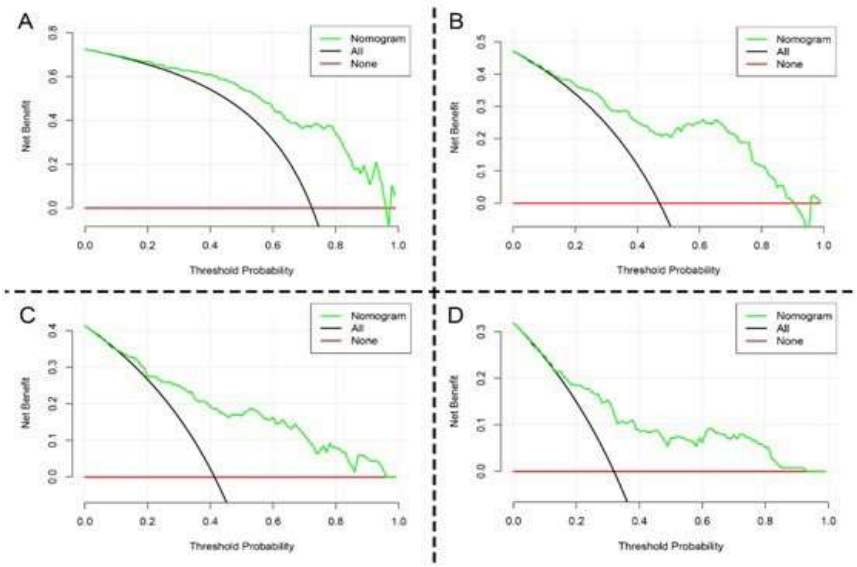
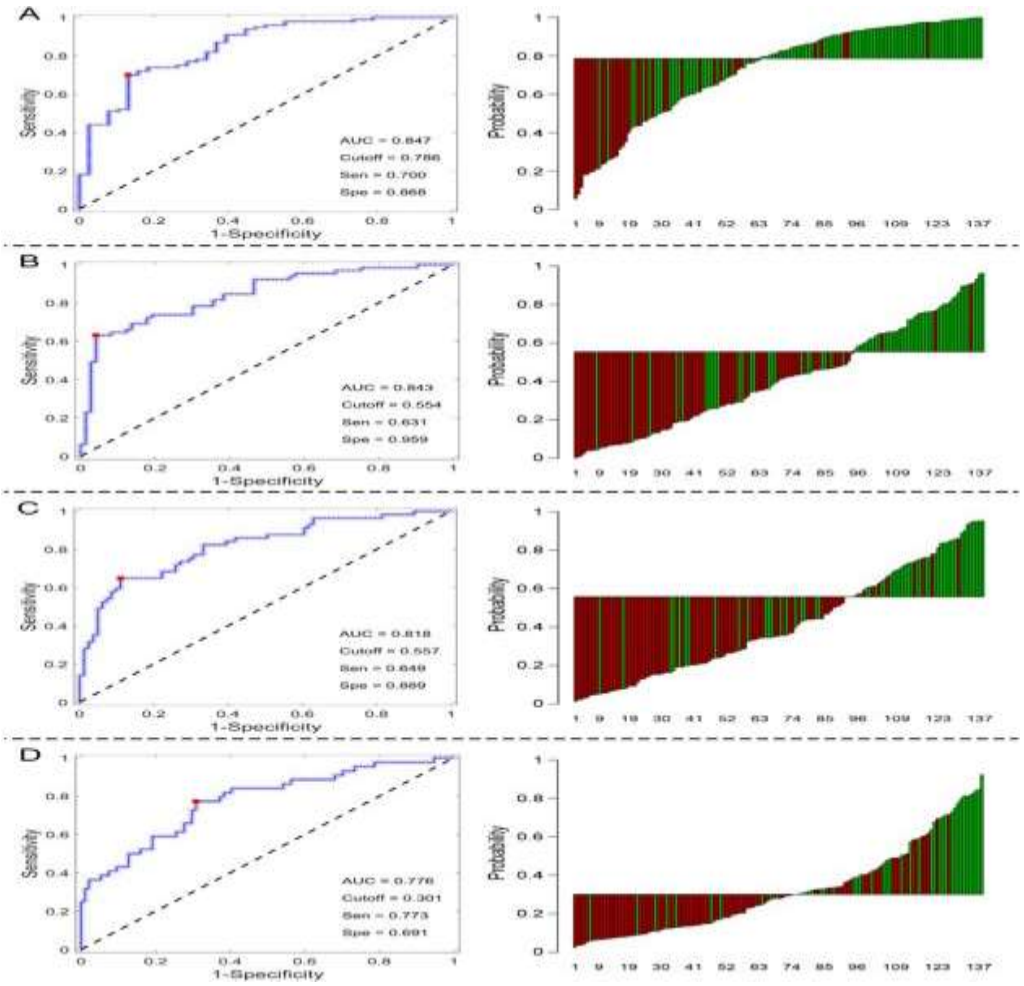


Figure 3. Decision curve analysis (DCA) of the developed nomograms indicating their respective usefulness.

The y-axis in figure 3 shows the net benefit. The x-axis represents the threshold probability. Threshold probability was the probability where the expected benefit with treatment equalled to the expected benefit without treatment. The green lines represent the developed nomograms. The black and red lines represent respectively the assumptions that all or none of the patients achieved effectiveness. For the 'any decrease' endpoint, our decision curve analysis (3A) showed that if the threshold probability was >0.2 and <0.95, then using the developed nomogram to predict effectiveness would confer greater benefit than treating either all or none of the patients. For <5 mg/dL endpoint, the threshold probability was >0.2 and <0.9 as shown in 3B. The threshold probability was >0.2 and <0.95 for 3 mg/dL (3C) and >0.2 and <0.85 for 2 mg/dL (3D).



Supplementary Figure 3. showed the receiver operating characteristic (ROC) curves and the corresponding waterfall plots of the developed nomograms for effectiveness. 3A showed that the any decrease model had an AUC of 0.847, 3B showed that the 5mg/dL model had an AUC of 0.843, 3C showed that the 3mg/dL model had an AUC of 0.818, and 3D showed that the 2mg/dL model had an AUC of 0.776.

5. Discussion

Obstructive jaundice in HCC patients is affected also by hepatic parenchymal damage [3,4,8,10]. The effective rates in our cohort were 73.19%, 49.24%, 41.30%, and 31.88%, respectively for any decrease in TBil, decrease to <5 mg/dL, 3 mg/dL, or 2 mg/dL endpoints. These outcomes were comparable to previous reports (Supplementary table 2) [1,3,4,6,8,9,14.] Clinical success rates in all malignant (excluding HCC or not) obstructive jaundice patients were better though (Supplementary table 2), [18,20,22,23] which was likely attributable to cirrhosis. We selected 4 weeks as the time of evaluation because it was a common practice. For patients and doctors who are willing to wait for longer, PTBD could be favored if the prediction models returned negative for their expected goal but positive for a less demanding target. However, we would remain conservative towards drainage if the prospect of any decrease after 4 weeks of adequate drainage was not satisfactory. MELD score and platelet level appeared in all 4 nomograms. They should both be reflecting the effect of cirrhosis. [14-16,18,29-33] It was once noted that all laboratory parameters except platelet count improved after effective drainage [1]. This implied that platelet count might be correlated to chronic cirrhosis independently from recent jaundice because independence could explain its survival from predictor selection algorithm. Predictive values of other liver function related [3,8,9,13,28] variables were not as consistent as MELD score and platelet. Influence of PVT in icteric type HCC patients is widely acknowledged (Supplementary table 1).[3,10-13,15,16] It was not in the prediction model for 2 mg/dL though. PVT was related to the 2 mg/dL goal and the trend of less patients with extensive PVT in more rigorous TBil target groups was conservative. However, the drop was more substantial from any decrease group to the <5 mg/dL group. (Table 1) It suggested that PVT was better a negative predictive factor. Extensive PVT portend an increased risk of no alleviation after PTBD. While all patients who reached the 5 mg/dL goal 4 weeks after PTBD could be able to achieve better TBil target although some might need more time, which correlated more closely to liver function and not PVT. It echoed the practice of some oncologists to prescribe anti-tumor treatment after achieving 5 mg/dL. Some studies indicated that for selected HCC patients with obstructive jaundice, local treatment could be performed without drainage. However, liver failure and death have been reported in these patients [1,5,10,11,13]. Predicting TBil changes would therefore be beneficial. To our knowledge, this study is the largest multicenter study on the subject. We performed analysis on several endpoints for physicians following different routines [1-24]. The models performed well in internal validation. DCA analysis showed that expected ranges of clinically beneficial prediction for all 4 endpoints covered considerably wide probability spaces that encompassed their respective effective rates (Figure 3). We would therefore like to suggest that patients with earlier stage HCC and obstructive jaundice be evaluated by these models when planning for treatment without drainage. Considering that the mean survival time could be between only 1 and 3 months in patients with advanced HCC and jaundice who were drained without improvement, [3,6,8,9,12,15-24] it would be worthwhile to assess the risk of inefficacy before deciding whether to perform even palliative drainage for them. The models also reminded us of the need for timely recognition and management of obstructive jaundice in HCC patients, as previously noted (Supplementary table 1) [1,5,10,12]. Only limited number of patients were included, which made external validation impractical, although internal validation showed good fit and DCA plots showed acceptable potential benefit. Another limitation was that the size and count of the tumor lesions were ranked. This was in conformity with current guidelines and to minimize error; however, it may have led to underestimation in the computational process.

6. Conclusions

In conclusion, the prediction models could facilitate preprocedural prediction of effectiveness of PTBD for HCC patients with HBV-related cirrhosis and obstructive jaundice. We analyzed several TBil targets so that the models could serve patients and doctors seeking data-based reference, either when they are looking for only best palliative care or aiming to treat the HCC eventually. Such help is relevant because PTBD is after all an invasive procedure.

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