Original Article

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Total bilirubin amount in drainage fluid can be an early predictor for severe biliary fistula after hepatobiliary surgery

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Summary **The ratio of the bilirubin concentration in abdominal drainage fluid to the serum bilirubin concentration (d-Bil/s-Bil) has been used as a predictor of biliary fistula (BF) formation after hepatobiliary surgery. The d-Bil/s-Bil ratio is highly influenced by the amount of drainage and is not always reliable, especially when the amount of drainage is large. In this study, the usefulness of the d-Bil/s-Bil ratio and total bilirubin amount in the drainage fluid (TBA) (bilirubin concentration in the drainage fluid x the amount of drainage) as predictors of severe BF (sBF) formation was evaluated retrospectively from the data of 306 patients who had undergone hepatobiliary surgery. Of the 306 patients, 201 patients were included in the training set and the remaining 105 in the validation set, to determine the best parameter to predict sBF formation after hepatobiliary surgery. Receiver-operating characteristic curve analysis revealed that the predictive power of TBA was superior to that of the d-Bil/s-Bil ratio throughout the postoperative period, and that the TBA on postoperative day (POD) 1 showed the highest discriminatory power in the training set (area under the curve, 0.789; cutoff value, 470 mg/day). The TBA on POD 1 also showed the highest predictive power for sBF formation in the validation set, with a sensitivity of 100%, specificity of 97.1%, and accuracy of 97.1%. In conclusion, TBA may be a more reliable predictor of sBF than the conventionally used d-Bil/s-Bil ratio. Early prediction of sBF may be useful for early removal of unnecessary prophylactic drainage tubes after hepatobiliary surgery.**

Keywords: Total bilirubin amount, biliary fistula, hepatobiliary surgery, drainage

1. Introduction

Despite the advances in the surgical and postoperative management techniques, the risk of development of biliary fistula remains a problem after complex hepatobiliary surgery (*1-5*). An undrained biliary fistula may be further complicated by abdominal abscess formation and sepsis, necessitating long-term drainage or even surgical intervention (*6*). Therefore, an abdominal drain is routinely placed prophylactically in many institutions to prevent this postoperative morbidity sequence (*7,8*). On the contrary, however, several recent studies have reported that prophylactic drainage after hepatic resection may not reduce morbidity, but may, in fact, increase the risk of reactive ascites and/or retrograde infections, resulting in prolongation of the patient's hospital stay (*9-15*). Early removal of drainage can minimalize the risk of drainage related infection without neglecting bleeding or obvious bile leakage. Thus, early removal, at the optimal time, of unnecessary abdominal drains is necessary even after complex hepatobiliary surgery.

The International Study Group of Liver Surgery (ISGLS) defined biliary fistula and classified it into three grades in 2011 (Table 1); biliary fistula after

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Table 1. The International Study Group of Liver Surgery classification of biliary fistula*

Definition	Bile leakage is defined as fluid with an increased bilirubin concentration in the abdominal drain or in the intra-abdominal fluid on or after postoperative day 3, or as the need for radiologic intervention (*i.e.*, interventional drainage) because of biliary collections or relaparotomy resulting from bile peritonitis. Increased bilirubin concentration in the drain or intra-abdominal fluid is defined as a bilirubin concentration at least 3 times greater than the serum bilirubin concentration measured at the same time.
Grade	
A	Bile leakage requiring no or little change in patients' clinical management.
B	Bile leakage requiring a change in patients clinical management (eg, additional diagnostic or interventional procedures) but manageable without relaparotomy, or a Grade A bile leakage lasting for >1 week.
C	Bile leakage requiring relaparotomy.

*Adapted from Koch 2011.

hepatobiliary and pancreatic surgery was defined as an at least threefold higher bilirubin concentration in the drainage fluid than the serum bilirubin concentration on postoperative day (POD) 3 or later, or as the need for radiologic or operative intervention resulting from biliary collections or bile peritonitis (*16*). However, the bilirubin concentration in the drainage fluid may be influenced by the amount of drainage, especially in patients with liver cirrhosis and those undergoing extended hepatectomy (*17*). Nevertheless, little is known yet about whether the bilirubin "concentration" is actually the most reliable measure of the risk of development of major biliary fistula or not (*18*). Therefore, this study sought to compare the predictive power of the ratio of the bilirubin concentration in abdominal drainage fluid to the serum bilirubin concentration (d-Bil/s-Bil), the conventionally used criterion proposed by the ISGLS, and that of the new parameter "total bilirubin amount", to determine the best measure for predicting severe biliary fistula formation requiring long-term management with drainage.

2. Materials and Methods

2.1. *Materials*

Data of a total of 306 patients who underwent liver resections or bilioenteric anastomoses at Toranomon Hospital between January 2011 and January 2016 were retrospectively reviewed. Of the 306 patients, the initial 201 patients who underwent surgery from January 2011 through March 2015 were included in the training cohort to determine the cutoff values of the drainage parameters, and the remaining 104 patients who underwent surgery between April 2015 and January 2016 were included in the split-sample internal validation cohort.

Data obtained from the clinical records were used to calculate the d-Bil/s-Bil ratio, the conventionally used criterion recommended by the ISGLS, and the total bilirubin amount (bilirubin concentration in the drainage fluid x the amount of drainage) on PODs 1, 3 and 5. The predictive powers of the two parameters for severe biliary fistula formation were compared to identify the best clinical measure for this prediction. The study was conducted with the approval of the institutional review board of Toranomon hospital, and all the analyses were performed in accordance with the ethical guidelines for clinical research at the hospital.

2.2. *Surgery*

Hepatic parenchymal transection in all the patients was performed by the clamp crushing method using Pringle's maneuver or by the microwave precoagulation method without vascular occlusion. Bile leakage was routinely checked at the final step of the parenchymal transection, and a tissue sealant sheet or fibrin glue was applied to the raw surface of the liver. Bilioenteric anastomosis was performed by intermittent suture using 5-0 absorbable suture. A closed suction drain was routinely placed near the transected plane or behind the biliary anastomosis. Both the amount of drainage and the bilirubin concentration in the drainage fluid (and serum) were measured on alternate days (PODs 1,3,5,...) until the drain was removed.

2.3. *Postoperative management*

A prophylactic antibiotic, cefmetazole sodium, was routinely administered for 2 to 5 days after the surgery. The drain was usually removed within 5 days of surgery when the d-Bil/s-Bil ratio was < 3, the amount of drainage was < 200 mL/day, and there was no evidence of infection. In case that the drainage was poor and with less fluid, the drain was removed at that point.

Biliary fistula was defined according to the ISGLS classification. The total bilirubin amount (TBA) was calculated by multiplying the drainage volume by the bilirubin concentration of the drainage fluid. The d-Bil/s-Bil ratio was calculated by dividing the bilirubin concentration of the drainage fluid by the serum bilirubin concentration.

Table 2. Patient characteristics and data related with biliary fistula in training set

Items	sBF* (*n* = 14)	Non-sBF (*n* = 187)	*P*
Male/female	9/5	131/56	0.764
Age (years)	68 (58 – 76)	67 (60 – 73)	0.487
BMI (kg/m^2)	26.4 (19.8 – 22.0)	22.3 (19.9 – 24.6)	0.611
Operation type			0.001
Hepatectomy	13	87	
Biliary tract reconstruction	1	100	
Blood loss	765 (474 – 1107)	531.5 (250 – 1038)	0.253
Operation time	307.5 (208 – 381)	271 (175 – 370)	0.364
Grade of BF			
A		52	
B	13		
C	1		
Duration of drainage (d)	20 (15 – 30)	8 (6 – 10)	< 0.001
Discharg bilirubin concentration (mg/dL)			
POD1	6.4 (1.5 – 40.6)	1.1 (0.9 – 1.6)	0.001
POD3	4.9 (1.8 – 20.4)	1.7 (1.3 – 2.6)	0.002
POD5	8.0 (3.0 – 30.5)	2.0 (1.3 – 2.9)	< 0.001
Discharge amount (mL)			
POD1	277 (214 – 463)	175 (95 – 294)	0.026
POD3	66 (24 – 191)	50 (15 – 138)	0.388
POD5	114 (26.5 – 171)	49 (8.5 – 186.5)	0.483

Data are median (interquartile range) or numbers of patients unless otherwise indicated. *Biliary fistula was defined according to the international study group of liver surgery classification. *Abbreviations*: sBF, severe biliary fistula; BMI body mass index; POD postoperative day.

2.4. *Statistical Analysis*

Data are expressed as median with range. Statistical analysis was performed using the Mann–Whitney *U* test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate.

The receiver operating characteristic (ROC) curve was used to determine the predictive powers of the TBA and d-Bil/s-Bil ratio for severe biliary fistula formation (grade B or greater according to the ISGLS classification) in the training set, and the predictive powers of these drainage parameters were then compared in the validation set. All data were analyzed using SPSS, version 13.0 (SPSS, Chicago, IL). $P < 0.05$ was considered as denoting statistical significance, and all the tests were two-sided.

3. Results

The 201 patients of the training cohort consisted of 100 patients who underwent hepatic resections and 101 patients who underwent bilioenteric anastomoses. Biliary fistula (of any grade) was observed in 66 (32.8%) patients, including grade A biliary fistula in 52 (25.8%) patients, grade B biliary fistula in 13 (6.4%) patients and grade C biliary fistula in one (0.5%) patient. There was only one patient with late-onset bile leakage, who developed severe biliary fistula on POD 23 after discharge. The other patients were diagnosed as severe biliary fistula before removal of drainage. Drainage was mostly removed after POD 3. There were not any patients who developed sever postoperative hepatic failure. The incidence of severe biliary fistula was significantly higher in the hepatectomy group than in the bilioenteric anastomosis group in the training cohort. The drainage fluid bilirubin concentration and the amount of drainage on POD 1 were significantly higher in the patient group with severe biliary fistula formation than in the patient group not showing severe biliary fistula formation. On the other hand, amounts of drainage on POD 3 and POD 5 were equivalent between the two groups (Table 2). TBA both after hepatectomy and after bilioenteric anastomoses had similar tendency in non-severe biliary fistula group, though in severe biliary fistula group, TBA after bilioenteric anastomoses were lower.

Table 3. Predictive power for severe biliary fistula in training set

Items	AUC	*P*	Cut-off value
Bilirubin concentration ratio			
POD1	0.701	0.005	3.3
POD3	0.636	0.106	3.2
POD5	0.712	0.012	5.4
Total bilirubin amount			
POD1	0.789	0.001	470
POD3	0.665	0.007	923
POD5	0.776	0.001	469

Abbreviations. POD, postoperative day; AUC, area under the curve; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 3 and Figure 1 show the results of the ROC analysis conducted to determine the predictive powers of the d-Bil/s-Bil ratio and TBA for severe biliary fistula formation. The area under the curve (AUC) was the highest on POD 1 for TBA (AUC, 0.789) and on POD 5 for the d-Bil/s-Bil ratio (AUC 0.712). The cutoff value of the TBA on POD 1 was 470 mg/day (positive

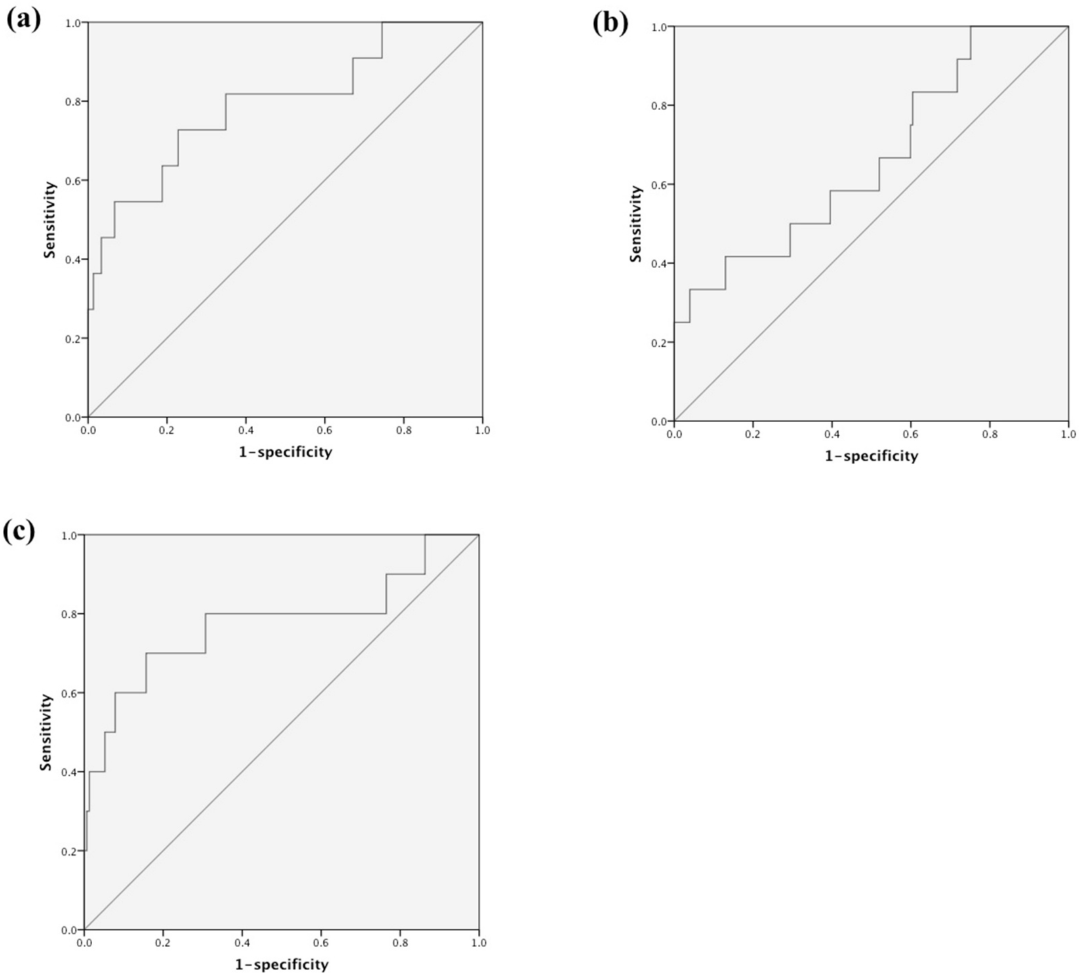

Figure 1. Receiver-operating characteristic curve of the total bilirubin amount. (a), Total bilirubin amount on POD 1 (AUC 0.789); **(b)**, Total bilirubin amount on POD 3 (AUC 0.665); **(c)**, Total bilirubin amount on POD 5 (AUC 0.776).

Table 4. Patient characteristics and data related with biliary fistula in validation set

Items	sBF* (*n* = 5)	Non-sBF (*n* = 99)
Male/female	5/0	66/33
Age (years)	65 (59 – 69)	67 (62 – 74)
BMI (kg/m^2)	20.3 (19.9 – 24.5)	21.2 (19.5 – 24.1)
Operation type		
Hepatectomy	3	63
Biliary tract reconstruction	2	36
Blood loss	950 (426 – 978)	851.5 (479 – 1390)
Operation time	238 (184 – 285)	246 (175 – 330)
Grade of BF		
A		13
B	5	
C	0	
Duration of drainage (d)	32 (34 – 65)	5 (4 – 7)
Discharge bilirubin concentration (mg/dL)		
POD1	52.3 (9.4 – 83.9)	1.2 (0.9 – 2.1)
POD3	18.1 (6.9 – 19.6)	1.85 (1.1 – 2.8)
POD5	3.4 (3.4 – 5.6)	1.9 (1.1 – 2.9)
Discharge amount (mL)		
POD1	330 (280 – 473)	176.5 (102 – 270)
POD3	72 (31 – 145)	53.5 (25 – 220)
POD5	181 (155 – 212)	50 (13 – 170)

Data are median (interquartile range) or numbers of patients unless otherwise indicated. *Biliary fistula was defined according to the international study group of liver surgery classification. *Abbreviations*: sBF, severe biliary fistula; BMI body mass index; POD postoperative day.

Table 5. Predictive power of drainage variables for sever biliary fistula in validation set

Items	Cut-off value	Sensitivity	Specificity	Accuracy	LR+	LR−
Bilirubin concentration ratio						
POD1	3.3	26.7	98.9	88.5	23.7	0.74
POD3	3.2	16.7	97.6	83.5	7.08	0.85
POD5	5.4	14.3	94.0	86.5	2.39	0.91
Total bilirubin amount						
POD1	470	100	97.1	97.1	34	0
POD3	923	N/A	N/A	N/A	N/A	N/A
POD5	469	0	92.8	91.4	0	1.08

Abbreviations: POD, postoperative day; LR+ positive likelihood ratio; LR- negative likelihood ratio; NA, not assesible.

likelihood ratio, 3.10; negative likelihood ratio, 0.36), and that of the d-Bil/s-Bil ratio on POD 5 was 5.4 (positive likelihood ratio, 6.95; negative likelihood ratio, 0.54). Of the 6 tested variables, TBA on POD 1 showed the highest predictive power for severe biliary fistula formation, based on the AUC value.

The clinical usefulness of the cutoff values determined in Figure 1 was then tested in the validation cohort. Table 4 reveals the demographic and clinical characteristics of the validation group. Of the 105 patients, biliary fistula formation was observed in 18 (17.1%) patients, including 13 patients who developed grade A biliary fistula and 5 who developed Grade B biliary fistula. Table 5 shows the predictive power of each of the aforementioned cutoff values in the validation set.

Of the tested variables, the TBA on POD 1 showed the highest sensitivity (100%) and specificity (97.1%), with an accuracy of 97.1%, for severe biliary fistula formation. The positive likelihood ratio was 34 and the negative likelihood ratio was 0. On the other hand, the d-Bil/s-Bil ratio had good specificity on PODs 1, 3 and 5 (98.9%, 97.6%, 94%), but the sensitivity was insufficient.

4. Discussion

In the present study, the predictive power of a new measure, the TBA in the drainage fluid, was compared with that of the conventionally used d-Bil/s-Bil ratio for severe biliary fistula formation after hepatobiliary surgery. The ROC curve analyses confirmed the superior predictive power of the TBA to that of the d-Bil/s-Bil ratio on PODs 1, 3 and 5, and revealed that TBA > 470 mg/day on POD 1 was the most sensitive measure to predict the formation of severe biliary fistula requiring continuous drainage, in both the training set and the validation set.

Prophylactic placement of an abdominal drain after hepatobiliary surgery can be useful for early detection of hemorrhage, biliary fistula formation, or infection. It can also be useful for the treatment of these complications (*7,8*). With the recent advances in surgical and perioperative management techniques, however, several studies have suggested that prophylactic placement of a drain is not always necessary after hepatobiliary surgery and that prophylactic drainage may, in fact, increase the risk of complications, including retrograde infection (*19*). Because late-onset bile leakage is relatively rare and difficult to predict (*20*), these authors have recommended against the routine use of prophylactic abdominal drains after hepatobiliary surgery.

Yamasaki *et al.* proposed the "3 x 3 rule" (drainage fluid bilirubin concentration less than 3 mg/dL on day 3 after the operation) as an accurate criterion for the removal of a prophylactically placed drain after liver resection (*21*). Tanaka *et al.* calculated the drainage fluid/serum bilirubin concentration ratio multiplied by the volume of the drainage fluid, and determined that a reliable cutoff value for this parameter on POD 2 was 200 (*18*). Although some authors have focused on the volume of discharge drainage to determine the cutoff value for removal of a prophylactically placed drain, the predictive power of the total amount of bilirubin drained has not yet been investigated. In this study, the drainage fluid bilirubin concentration on POD 1, 3, and 5 were significantly higher in the patient group with severe biliary fistula formation than in the patient group not showing severe biliary fistula formation. On the other hand, amounts of drainage on POD 3 and POD 5 were equivalent between the two groups. This may be an evidence of that the bilirubin concentration in the drainage fluid may be influenced by the amount of drainage. That is, the effusion increases over time, and the bilirubin concentration may change.

The novelty of the current study lies in the comparison of the actual predictive powers of the conventionally used criterion of the d-Bil/s-Bil ratio and the TBA on PODs 1, 3 and 5 for severe biliary fistula formation, and in the validation of the measure in a different study population. As shown in both in Table 3 and Table 5, the TBA showed a better predictive power than the d-Bil/s-Bil ratio for severe biliary fistula formation, and the TBA on POD 1 showed the highest predictive power. However, in this very early period, the problem of false positive should be concerned. In fact, the false positive rate was 2.9%, and this is sufficient as a predictor. Moreover, since patients who have false positive results will be re-assessed on POD 3 and receive removal of drains, the negative effect may be minimal.

These results suggest that the risk of severe biliary fistula formation could be predicted or detected from the TBA on POD 1, and that TBA may be a direct parameter that shows the severity of biliary fistula. That is, the greater TBA increases, the severer the biliary fistula becomes. Therefore, TBA may also serve as a criterion for the removal of unnecessary prophylactic drains. Migita *et al* (*22*). reported that retrograde drain infection could be detected from as early as POD 2 after surgery, and that early prediction of a drain-related infectious complication sequence can aid in the decision making process during postoperative management.

Limitations of this study include its retrospective nature and its being based on data from a single institution. On the other hand, the clinical management procedures were constant during the study period and similar outcomes were confirmed in both the training set and the validation set. The current results are clinically important in that early prediction of severe biliary fistula formation might be possible with measurement of the TBA. Because the bilirubin concentration in the drainage fluid is highly influenced by the amount of drainage, TBA may serve as a more accurate and direct measure of the amount of bile leakage, which might determine the risk of severe complication sequences.

It is better to differentiate the bile leak situations, such as hepatectomy without bilioenteric anastomoses, hepatectomy with bilioenteric anastomoses, and bilioenteric anastomoses. Since the incidence of severe biliary fistula was low in each situation, it was impossible to do this analysis in this study. A validation study using a larger prospective database is warranted to confirm the current results. However, we think TBA is a direct parameter and thus may not be affected by the reasons and mechanism for biliary fistula.

In conclusion, TBA may be a more reliable measure for predicting severe biliary fistula formation than the conventionally used d-Bil/s-Bil ratio. Early prediction of severe biliary fistula formation may allow early removal of unnecessary prophylactic drains placed after hepatobiliary and pancreatic surgery.

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