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Research Article

Hepatic marker combination provides relevant score to predict severe morbidity after colorectal metastases-related major hepatectomy

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ABSTRACT

Background and objectives: After hepatic resection, liver failure is not diagnosed until the postoperative day-5. The aim was to identify a biomarker predictive of severe morbidity, the day after major hepatectomy.

Methods: This retrospective study included patients undergoing major hepatectomy for colorectal metastases, plasma hepatic marker concentrations being determined at postoperative day-one. Outcomes were 30-day severe morbidity (Dindo III to V) and grade C post-hepatectomy liver failure.

Results: A total of 433 patients were included. Thirty-day severe morbidity, 90-day mortality and grade-C post-hepatectomy liver failure rates were 15.5%, 2.5% and 2.5% respectively. Using cut-offs determined by receiver operating characteristic curves the association of serum bilirubin ≥ 2.1 mg/dL (≥ 2 N) and aspartate-amino-transferase ≥ 450 IU/L (≥ 10 N) was selected for the best biochemical predictors of severe morbidity (sensitivity 38%, specificity 94%) and post-hepatectomy failure (sensitivity 100%, specificity 91%). In multivariate analysis, this score was independently associated with severe morbidity (HR = 5.98, 95% IC 2.65-13.89; P < 0.0001)

Conclusions: The association of plasma bilirubin ≥ 2.1 mg/dL and aspartate-amino-transferase ≥ 450 IU/L is identified as a relevant predictor of severe morbidity and post-hepatectomy failure as early as the first postoperative day after major hepatectomy for colorectal metastases.

Introduction

Improvements in hepatic surgery, perioperative management and patient selection have extended the indications for major hepatectomy for colorectal metastases [1-3]. Although mortality after liver surgery diminished over the past decades ranging from 0 to 8.2%, morbidity has remained substantial, still ranging between 30 and 40% [4, 5]. Knowledge of the incidence as well as risk factors may be useful for the early diagnosis of complications resulting in adequate treatment. Although it is not a frequent occurrence, post-hepatectomy liver failure (PHLF) can be a major cause of morbidity and mortality [6, 7]. In case of liver failure, conventional biochemical liver function tests evaluated by routine plasma bilirubin level and prothrombin time index have been widely used with various cut-off values at different postoperative time points. Some studies applied the “50-50” criteria at postoperative day 5

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[8, 9]. Alternatively, another group showed that a peak bilirubin of more than 7.0 mg/dl at any time-point accurately predicts liver-related death and worse outcomes after major hepatectomy [10]. More recently, the International Study Group for Liver Surgery (ISGLS) has recently proposed a definition for PHLF by using serum bilirubin and prothrombin time index on day 5 [11, 12]. Regardless of which definition is applied, the timing of the measurement of these variables in the postoperative period is inconsistent and hepatic failures are not identified until rather a late time within the postoperative course. We hypothesized that biochemical variables may help identify severe complications at postoperative day 1 (POD1) after a major hepatic resection. Most studies have failed to identify any biochemical marker at POD 1 that is independently associated with severe morbidity. Initial postoperative lactate concentration was recently found to be an early reliable predictor of postoperative outcome after hepatectomy [13]. The prognostic value of this factor has been reported widely following pancreatic resection, colorectal surgery and cardiac surgery [14-16]. However, arterial lactate concentration is not determined routinely after hepatic surgery, since obtaining arterial blood is more invasive than peripheral venous puncture. Despite a dramatic decrease in mortality rates following hepatic resection during the last 10 years, morbidity such as intra-abdominal sepsis, biliary complications and PHLF challenging [17, 18]. Technical improvements in the field of liver surgery and oncology have increased the possibility to extend the indication and selection criteria for performing major hepatectomy, leaving a small remnant liver. Thanks to progresses in volumetric measurements and portal vein embolization, hepatic surgery has become more and more aggressive with particular indications in chemotherapy-related liver lesions [19]. Although increasing overall survival, occurrence of PHLF is the price to pay, with major complications, especially severe infections. However, diagnosis of these major complications is often delayed due to the current unique validated scores based on biological marker concentrations 5 days post-surgery [8, 9, 20]. Most studies have evaluated the postoperative kinetics of biochemical liver markers diminution among patients who did not experience any complication. For example, serum bilirubin, International Normalized Ratio (INR), ASAT and ALAT show marked augmentation immediately after surgery and usually return to normal values within the first 5 to 7 postoperative days [21]. Early detection of postoperative complications may be identified when these physiological changes do not occur but may still necessitate several days of follow up [22].The aim of this study was to identify reliable and easily available postoperative predictors of adverse outcomes after major hepatectomy, as early as the first day post-surgery.

Materials and Methods

Patient Demographics

The present study is a retrospective bi-centric study. Patients were enrolled between October 1996, and January 2015, by 2 tertiary care university hospitals (Haut-Leveque hospital, Pessac; Rangueil hospital, Toulouse).

All included patients underwent an elective major hepatectomy, defined as resection of three or more hepatic segments. Patients with hepatic chronic liver disease were excluded, as pre-existing chronic liver disease would affect the postoperative course of liver function test. Patients undergoing a resection for non–colorectal liver metastases, hepatocellular carcinoma or hilar cholangiocarcinoma were excluded to avoid confounding factors related to background liver dysfunction. Those for whom biochemical data were incomplete were also excluded. Basic demographic and clinico-pathologic data were collected and recorded in the database. Explanatory variables were pre-operative (including age, sex, body mass index, comorbidities, preoperative chemotherapy, preoperative portal embolization) and intraoperative variables (including simultaneous primary tumor resection, associated procedures, inflow occlusion, duration of surgery, requirement for red blood cells transfusion on or before postoperative day 2).

This study was conducted according to the French rules (Loi Jardé November 2017) and the recommendations of CNIL (Comité National Informatique et Liberté) for the extraction and the treatment of the data anonymously. According to these rules and due to the retrospective design of the study, obtaining the informed consent was not necessary for the processing of personal data by all patients. Moreover, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Postoperative course

Biological data

Blood samples were drawn routinely 1, 3, 5 and 7 days after operation. Biochemical blood test results on POD 1 were included in the analyses: serum bilirubin, aspartate-amino-transferase (ASAT), alanine-amino-transferase (ALAT) and prothrombin time (PT) index.

The institutional laboratory reference range for normal plasma bilirubin, ASAT, ALAT and PT index were 0.17 - 1.05 mg/dL, 10-45 IU/l, 21-50 IU/L and 70-100% respectively.

Postoperative complications

Postoperative complications, recorded at 30 days, included any adverse event that occurred after hospital discharge and were reported according to the classification proposed by Dindo and colleagues [17]. Minor complications defined as grades I and II were the adverse events with no or minimal impact on postoperative course and were consequently not recorded. Life-threatening complications defined as grades III and IV were considered as major postoperative morbidity. Postoperative mortality was defined as any death within 90 days of operation or during the same hospital stay. Postoperative mortality related to liver failure itself or to multisystem organ failure including liver failure was specified. Length of stay was calculated from the first postoperative day through the day of discharge or death. PHLF was defined as an increased INR with hyperbilirubinemia at 5 days or more following surgery.

Postoperative patient groups

Briefly, patients were classified into two groups: Group A if they had a normal clinical course or an inconsequential transient elevation of liver function tests; The Group B included patients who required a change in their clinical management, e.g. a longer stay in the high-dependency unit, the use of diuretics for ascites, non-invasive ventilation etc.; Group C patients that need invasive management, e.g. the use of inotrope/invasive ventilation and percutaneous catheter drainage of ascites/pleural

effusion. Additionally, the "50-50 criteria" as proposed by Balzan and colleagues (8) in predicting death resulting from PHLF was also reported.

Study endpoints

The primary endpoint of the study was postoperative outcome defined by severe morbidity (grades III to V). Secondary endpoints were PHLF and length of stay (LOS).

Statistical analysis

Continuous variables were expressed as median values with interquartile range (IQR). Discrete variables were expressed as absolute values and percentages (%). Dindo-Clavien morbidity grade was treated as a categorical variable. Total bilirubin, prothrombin time, ASAT and ALAT were treated as categorical variables using cut-offs determined by receiver operating characteristic (ROC) curves. The accuracy of biological variables to predict severe morbidity was measured by the area under the receiver operating characteristic curve (AUROC). To adjust biological variables effect for significant confounding factors, uni- and multivariate logistic regression analysis were performed to identify independent predictors of severe morbidity. Association with *p* values <0.05 were considered significant. Student *t test, chi square* test, and Fisher exact tests were used for univariate analysis where needed. Multivariate analysis was performed using logistic regression models. Odds ratio (OR) with 95% confidence intervals (95% CI) derived from logistic regression were calculated (R software version 2.15.0).

Results

Patient's characteristics

A total of 462 patients underwent major liver resection for colorectal metastases during the study interval of 19 years. Laboratory values on POD 1 were available for a total of 433 patients. Baseline patient characteristics are summarized in (Table 1). Preoperative chemotherapy was performed in 348 patients (80.7%) with 160 (37%) having received > 8 cycles. Seventy-six patients (17.6%) had undergone a previous liver resection, including 40 patients with a two-stage hepatectomy (9.2%). The most frequently performed operative procedure was a right hepatectomy with, or without resection of segment I (n=328, 75.8%). A left hepatectomy with, or without resection of segment I was performed in 94 patients (21.7%). Portal triad clamping was performed in 343 patients (81.1%) with a median time of 30 min (6-82 min). Radiofrequency was combined to liver resection in 44 patients (10.2%).

Table 1: Characteristics of the 433 patients with major hepatectomies for colorectal metastases assigned to analysis

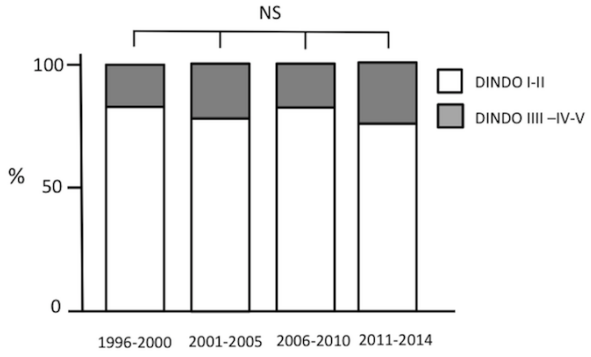
Clinico-pathologic variables	**Value**
Patients	
Age, *yr, median (range)*	63 (32-85)
Male gender, *n (%)*	244 (56,4)
Diabetes, *n (%)*	46 (10.8)
ASA class, *n (%)* 1 2 3	 79 (18.9) 297 (70.9) 43 (10.3)
BMI, *kg/m2, median (range)*	25,0 (15-43)
Primary tumor, *n (%)* Colon Rectum	 279 (65.2) 149 (34.8)
Preoperative chemotherapy, *n (%)*	348 (80.7)
Preoperative PVE, *n (%)*	169 (39.4)
Operative factors	
Simultaneous primary tumor resection, *n (%)*	7 (1,6)
Total operative time, *min*	241.5 (± 61.1)
Associated procedure, *n (%)*	83 (19.3)
Inflow occlusion, *n (%)*	343 (81.1)
Blood transfusion, *n (%)*	113 (26.8)
Steatosis >30%, *n (%)*	51 (12.4)
Laboratory test	

POD1 total bilirubin, *mg/dl, median (range)*	1.23 (0.35-7.9)
POD1 PT, *% median (range)*	65 (33-100)
POD1 ASAT, IU/L, *median (range)*	415 (45-4410)
POD1 ALAT, IU/L, *median (range)*	421 (42-2635)
Postoperative course, *n (%)* Dindo III-IV-V	78 (18)
Mortality, *n (%)*	11 (2.5)
PHLF (Grade C), *n (%)*	11 (2.5)
LOS, *day, median (range)*	11 (5-72)

ASA:American Society of Anesthesiologists; BMI, body mass index; PVE, portal vein embolization; PT, prothrombin time; POD, post-operative day: PHLF: post-hepatectomy liver failure; LOS: length of stay.

Morbidity and complications

Overall morbidity occurred in 228 patients (52.6%). Major complications occurred in 67 patients (15.5%), with the following grades: grade IIIa (n=41; 9.5%), grade IIIb (n=7; 1.5%), grade IV (n=19; 4.5%). The 90-day mortality rate was 2.5 % (11 patients). Grade C PHLF developed in 11 patients (2.5%) and was associated with perioperative death in 7 patients (64%). The median LOS was 11 days (5-72). Of note, the rate of complications was similar regardless the period of recruitment, which was split into four quartiles (supplemental figure 1).



Supplemental figure 1:
Proportion of postoperative severe morbidity (Dindo score III to V) (present Grey bar; absent White bar) depending on the period of inclusion (1996-200 = 35; 2001-2005: n =; 2006-2010: n = and 2011-2014: n =) (Chi2 and Fisher exact tests $0.31 < p < 1.00$; NS: non-significant).

Impact of the biological data at POD 1 on the postoperative severe morbidity

Median ASAT and ALAT levels were 398 IU/L (Inter Quartile Range/IQR: 45-4410) and 415 IU/L (IQR: 42-2635), respectively, in patients with no complications or grade I-II complications, and 489 IU/L (IQR: 165-3625) and 463 IU/L (IQR: 111-2624), respectively, in patients with grade III-V complications. Bilirubin levels and PT index were 20 mg/dl (IQR: 6-135) and 66 % (IQR: 37-100) in patients with no complications or grade I-II complications, respectively, 31 mg/dl (IQR: 7-100) and 63 % (IQR: 33-100) in patients with grade III-V complications, respectively.

To identify cut-offs for biological indicators of severe morbidity on POD 1, a ROC curve was constructed. The best cut-off values on POD 1 for ASAT, ALAT, bilirubin and PT index in determining the risk of severe morbidity were 450 IU/L (10 N), 500 IU/l (10 N), 2.1 mg/dL (2 N) and 70 % respectively. On univariate analysis, bilirubin, ASAT and PT index expressed as categorical variables using these cut-offs were associated with increased severe morbidity ($p<0.001$, $p=0.001$, $p=0.003$ respectively) (Table 2). Demographic and preoperative variables were found to be significantly associated with severe morbidity, including male gender, an ASA (American Society of Anesthesiologists) class ≥ 3, a body mass index (BMI) above 25 kg/m^2 and simultaneous primary tumor resection and preoperative portal vein embolization. Intraoperative variables that significantly increased the risk of severe morbidity were the duration of surgery above 240 minutes, associated procedures, inflow occlusion and the requirement for blood transfusion. Of all these factors, only the POD 1 total bilirubin, ASAT and PT index demonstrated an independent association with severe morbidity on multivariate analysis ($p=0.0021$, $p=0.013$, $p=0.010$, respectively) (Table 2).

Table 2: Uni- and multivariate analysis of risk factors for postoperative severe morbity in 433 patients with major hepatectomies for colorectal metastases

	Univariate analysis	Multivariate analysis
Variable	**Dindo III-V (n=78)**	**Dindo III-V (n=78)**

	HR	95%CI	p	HR	95%CI	p
Age (≥ 65 years)	1.16	(0.71-1.91)	0.55		-	
Male gender	**2.38**	**(1.40-4.18)**	**0.0022**	2.76	(1.32-6.06)	0.10
ASA class						
1						
2	**0.93**	**(0.48-1.83)**	**0.006**	0.72	(0.3-1.8)	0.14
3	**3.01**	**(1.28-7.1)**		2.72	(0.83-9.12)	0.10
BMI (> 25 kg/m^2)	**1.85**	**(1.10-3.17)**	**0.022**	1.02	(0.51-2.03)	0.95
Diabetes	1.12	(0.49-2.35)	0.77		-	
Preoperative chemotherapy	1.97	(0.98-4.40)	0.073		-	
Simultaneous primary tumor resection	**6.42**	**(1.39-33.22)**	**0.020**	4.82	(0.58-56)	0.17
Total operative time (> 240 min)	**2.08**	**(1.26-3.47)**	**0.004**	0.75	(0.36-1.53)	0.44
Pre-operative PVE	**1.74**	**(1.06-2.87)**	**0.028**	1.69	(0.84-3.43)	0.14
Associated procedure(s)	**2.08**	**(1.17-3.62)**	**0.011**	1.56	(0.69-3.46)	0.28
Inflow occlusion	**2.59**	**(1.21-6.41)**	**0.023**	2.43	(0.82-9.08)	0.14
Blood transfusion	**2.19**	**(1.29-3.67)**	**0.003**	2.76	(1.32-6.06)	0.10
Steatosis >30%	1.32	(0.62-2.64)	0.45		-	
POD1 bilirubin ≥ 2.1mg/dL	**4.59**	**(2.70-7.82)**	**<0.001**	**2.95**	**(1.48-5.89)**	**0.0021**
POD1 PT < 70%	**2.55**	**(1.41-4.84)**	**0.003**	**2.79**	**(1.31-6.32)**	**0.010**
POD1 ASAT ≥ 450 IU/L	**2.34**	**(1.42-3.92)**	**0.001**	**2.42**	**(1.22-4.93)**	**0.013**
POD1 ALAT ≥ 500 IU/L	1.36	(0.82-2.25)	0.23		-	

ASA indicates American Society of Anesthesiologists; BMI, body mass index; PVE, portal vein embolization; POD, post-operative day; PT, prothrombin time; Statistical significant values are indicated in bold.

Relationship between the combination of POD 1 bilirubin and ASAT values and post hepatectomy liver failure grade C or length of stay

The associated cut-off of bilirubin and ASAT values provided the best performing ROC curve for prediction of severe morbidity. The area under the ROC curve (AUC) for the model based on bilirubin was 0.73 (Figure 1). The cut-off value 2.1 mg/dL of bilirubin was chosen and provides a sensitivity of 61% and specificity of 82%. Similarly, the area under the ROC curve for the model based on ASAT was 0.72 with a sensitivity of 81% and specificity of 63% for values over 450 IU/L (Figure 2). The positive predictive value was 59% and the negative predictive value 87%. The prediction of severe morbidity and hepatic failure was more accurate when both variables were used in combination. Fifty-one patients (12%) had simultaneously bilirubin ≥ 2.1 mg/dL and ASAT ≥ 450 IU/L on POD 1. Among them, 30 developed major complications (59%), compared with 48 (13%) when only a single criterion was fulfilled (Figure 3). The overall mortality rate was 14% (n= 7) versus 2.5% (n=11).

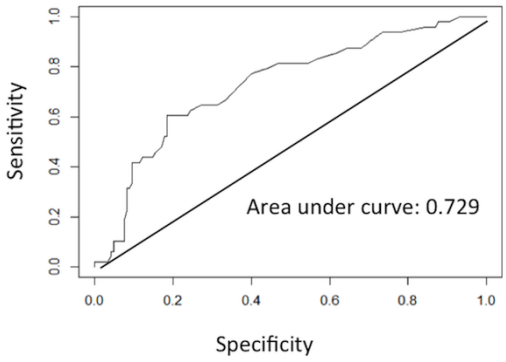


Figure 1: Receiver operative characteristic curve for serum bilirubin at post-operative day one as a discriminant of increased severe morbidity among patients with ASAT ≥ 450 IU/L (≥ 10 N) (n=195 patients)

Considering the prediction of PHLF grade C, the cut-off value of serum bilirubin and ASAT exhibited high sensitivity (100%) and specificity (91%). Among patients with PHLF grade C, 7 (64%) died of postoperative complications clearly related to liver dysfunction. The 4 patients who died and who did not fulfil both criterias did not develop hepatic insufficiency. Among the patients with 50-50 criteria on POD 5 (n =7), 4 fulfilled the score on POD 1. All (100%) had severe morbidity requiring intensive care and 2 (50%) died on postoperative period. On the other hand, patients with 50-50 criteria on POD 5 but who did not fulfil the score on POD 1 (n= 3) had only grade II complications.

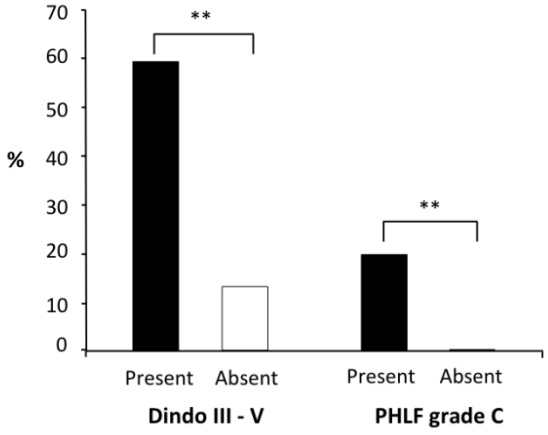


Figure 2: Receiver operative characteristic curve for ASAT at post-operative day one as a discriminant of increased severe morbidity among patients with serum bilirubin ≥ 2.1 mg/dL (≥ 2N) (n=93 patients)

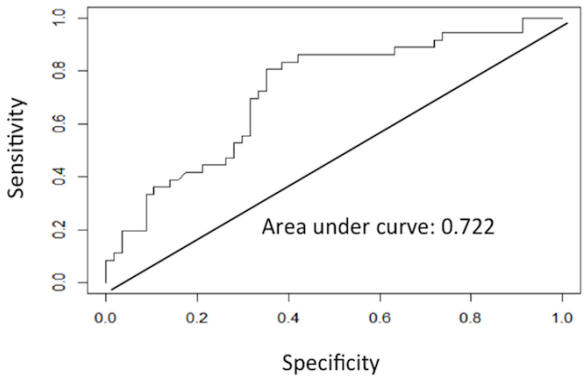


Figure 3: Postoperative severe morbidity (Dindo score III to V) and posthepatectomy liver failure (PHLF) grade C after major hepatectomy, stratified by biological post-operative day one score combining "serum bilirubin level ≥ 2.1 mg/dL + ASAT level ≥ 450 IU/L (bilirubin ≥ 2N + ASAT ≥ 10N) (score present: black bar; score absent ; white bar - ** : p< 0.001).

This biological tool was included in a multivariate logistic regression model with the other variables. Using these cut-off values, the score combining serum bilirubin ≥ 2.1 mg/dL (≥ 2N) and ASAT ≥ 450 IU/L (≥ 10 N) was independently associated with severe post-operative morbidity (Dindo score III to V) (HR = 5.98, 95% IC 2.65-13.89; P < 0,0001). Using the same score, the median duration of hospital stay was 21.5 days (6-63) versus 11 days (5-72) (Figure 4).

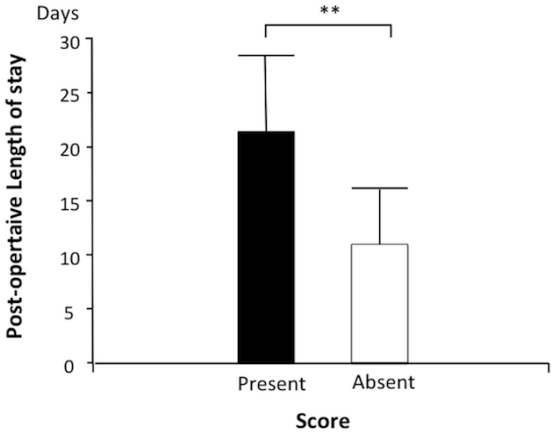


Figure 4: Postoperative length of stay (LOS) after major hepatectomy, stratified by the biological post-operative day one score combining "serum bilirubin level ≥ 2.1 mg/dL + ASAT level ≥ 450 IU/L (bilirubin ≥ 2N + ASAT ≥ 10N) (score present Black bar; score absent; white bar – mean ± SD - ** p< 0.001).

Discussion

The purpose of this study was to identify an early predictor of postoperative severe morbidity after major hepatectomy. A POD 1 bilirubin level ≥ 2.1 mg/dL (≥ 2N) in combination with ASAT ≥ 450 IU/L (≥ 10N) was associated with a significant increased risk for major postoperative complications. Analysis of the ROC curves revealed that the association of bilirubin and ASAT levels rendered the best-fit curve, with an AUC of 0.73. Considering severe morbidity, this score retained significance in a multiple regression model.

In this study, ASAT alone at POD 1 was significantly associated with severe morbidity. However, analysis of the ROC curve revealed a poor ability to predict severe morbidity from uneventful postoperative course (AUC: 0.638). Bolewaski et al. found similar results (AUC: 0.61) [23]. They also demonstrated that a peak increase in ASAT levels was not correlated with either morbidity or severe morbidity, whether ASAT was entered in the prognostic models as a linear variable or as a categorical variable on the basis of cut-offs. Even extreme values of ASAT (>1000 IU/L) did not discriminate severe morbidity. Moreover, transaminase increase was not accurate to predict poor outcome. In fact, transient biochemical changes are commonly observed after uncomplicated hepatectomy [22]. The rise in transaminases occurs between days 1 and 2 and reflects hepatocyte injury. A decrease to normal levels is achieved between day 7 and 10 in the absence of complications. Preoperative and intraoperative conditions may disturb the results of postoperative blood tests. Liver ischemia induced by manipulation of the liver, temporary inflow occlusion, non-anatomical resections, bleeding and hemodynamic conditions, which are frequently hypotensive, are associated with a rise in transaminases. In fact, the POD 1 transaminases peak is multifactorial and often reflects a transient pathologic situation, with a low impact onthe clinical outcome. However, as few cases may be predictive of severe irreversible pathologic situation, POD 1 transaminases dosage is part of the routinely needed biological exams.

As transaminase levels alone are not predictive of severe post-operative failure, we hypothesized that the concomitant use of bilirubin on POD 1 could be useful to detect this subset of population at risk. The meaning of the concomitant rise in transaminases and bilirubin on POD 1 remains unclear. The early total bilirubin increase might reflect a liver sideration as a result of a dramatic initial cytolysis or is the result of liver dysfunction. However, the cut-off value for POD 1 bilirubin ≥ 2.1 mg/dL associated with ASAT ≥ 450 IU/L exhibited moderate sensitivity to early detect overall major morbidity. In fact, major complications are the result of various physiopathological mechanisms. Bilioma and pleural effusion are common postoperative complications, which sometimes require radiologic or surgical drainage. For some patients, these severe complications may be associated with a high risk for liver failure. However, this risk remains mostly isolated with a good prognosis and without early concomitant hepatic failure. In the case of bilioma, many studies have assessed the relationship between bile leakage and surgical procedures such as exposure of the main glissonean sheath, cut surface management and repeated hepatectomy [24, 25]. Liver failure is often missing or may only appear once severe septic complications occur. Indeed, in this study, major morbidity observed in patients with no or minor biological changes on POD 1 relates solely to bilioma or pleural effusion with no life-threatening outcome. In fact, the grade associated with these complications, which depends on the treatment, may reflect specific medical practices or policies (post-surgery follow-up, placing a drain under local anaesthesia or under general anaesthesia or operate again) rather than the intrinsic severity of the complication. On the other hand, patients with major morbidity and underlying the score on POD 1 are more likely to develop liver failure or multi-system organ failure. This score is a meaningful definition of severe morbidity with physiopathology in close correlation with hepatic dysfunction. It could

define a point of no return that separates a moderate, reversible complication from a life-threatening one.

The cut-off values for bilirubin and ASAT in this study are in agreement with the literature. In a previous study analysing biochemical tests on POD 1, a cut-off value of 2.05 mg/dl of bilirubin was chosen for the prediction of hepatic complications and overall morbidity [26]. Another recent study reported a cut-off value of 450 IU/L for ASAT to predict severe morbidity [23]. ALAT levels were not predictive of postoperative morbidity or mortality in these studies highlighting the sole importance of ASAT.

There are two main methodological advantages of the present study. First, it was performed on a rather homogenous group of non-cirrhotic patients with normal baseline liver function undergoing major liver resections for colorectal metastases. Second, although the design was retrospective, biochemical parameters included in the analyses were performed routinely on POD 1 in all patients. Except for the '50-50' criteria on POD 5, previous study only focused on unique biochemical variables [10, 26, 27]. To our knowledge, this is the first study to propose the association of 2 postoperative biological variables in order to predict worse postoperative outcomes as soon as day 1 after major hepatectomy. Indeed, on day 5, it is often too late to improve the situation. High ASAT levels combined with elevated bilirubin on POD 1 should be considered as an alarm and require aggressive investigations to point at specific complications. These early investigations may include multiple bacteriological tests to identify bacterial ascites or pneumonia as well as Doppler-US and CT-scans to rule out vascular thrombosis or intra-abdominal collection. As it may be quite difficult to reliably detect the exact source of biological disturbance, we only focused on postoperative outcome related to biochemical changes, regardless of additional investigations, even if acknowledge that a perfect biological tool on POD 1 to accurately predict overall major morbidity is probably unrealistic.

The patient selection was carried out over two decades; however, we selected a homogenous population of colorectal cancer metastasis. Reports have shown a slight improvement of morbidity over long periods of study [4-5]. Indeed, the sensitivity and specificity to predict such morbidity is certainly increasing overtime due to better care management. The present biological score is an early easily accessible tool to strongly eliminate an associated severe hepatic failure, that was already available at the beginning of patient selection (this study), with the same methods and accuracy. Despite this new early-course predictor of severe morbidity after major hepatectomy further research is needed to identify preoperative predictors of postoperative morbidity and mortality.

Conclusion

In conclusion, this study highlights a simple and easy access test combining plasma bilirubin (≥ 2.1 mg/dL - ≥ 2N) and ASAT (≥ 450 IU/L - ≥ 10 N) that reliably identifies a population at risk of severe morbidity during follow-up of major hepatectomy. As a result, intensive care management might occur much early to contribute reducing the rate of postoperative liver failure and the length of stay.

Author Contributions

I: Conception and design: E. Buscail, A. Pontallier, C. Laurent, L. Chiche; II: administrative support: C. Laurent, L. Chiche; F. Muscari, V. Vendrely; III: provision of study materials or patients: All authors; IV: Collection and assembly of data: all authors; V: Data interpretation and analysis: All authors; VI: Manuscript writing: E. Buscail, A. Pontallier, S. Dabernat, C. Laurent, L. Chiche; VII: Final approval of the manuscript: all authors.

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