The "50-50 Criteria" on Postoperative Day 5

An Accurate Predictor of Liver Failure and Death After Hepatectomy

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Objective: To standardize the definition of postoperative liver failure (PLF) for prediction of early mortality after hepatectomy.

Summary Background Data: The definition of PLF is not standardized, making the comparison of innovations in surgical techniques and the timely use of specific therapeutic interventions complex.

Methods: Between 1998 and 2002, 775 elective liver resections, including 69% for malignancies and 60% major resections, were included in a prospective database. The nontumorous liver was abnormal in 43% with steatosis >30% in 14%, noncirrhotic fibrosis in 43%, and cirrhosis in 12%. The impact of prothrombin time (PT) <50% and serum bilirubin (SB) >50 μmol/L on postoperative days (POD) 1, 3, 5, and 7 was analyzed.

Results: The lowest PT level was observed on postoperative day (POD) 1, while the peak of SB was observed on POD 3. These 2 variables tended to return to preoperative values by POD 5. The median interval between hepatectomy and postoperative death was 15 days (range, 5–39 days). Postoperative mortality significantly increased in patients with PT <50% and SB >50 μml/L. The conjunction of PT <50% and SB >50 μmol/L on POD 5 was a strong predictive factor of mortality. In patients with significant morbidity, this "50-50 criteria" was met 3 to 8 days before clinical evidence of complications.

Conclusions: The association of PT <50% and SB >50 μml/L on POD 5 (the 50-50 criteria) was a simple, early, and accurate predictor of more than 50% mortality rate after hepatectomy. This criteria could be identified early enough, before clinical evidence of complications, for specific interventions to be applied in due time.

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Technical improvements in liver surgery during the last decade have resulted in an expansion of the indications for major hepatectomies, especially in high-risk patients with various underlying liver conditions (fibrosis, steatosis, or chemotherapy-induced injury).[1–6] However, the risk of postoperative liver failure (PLF) and fatal outcome have remained important concerns.[1,2,7] Although several clinical and biologic variables such as ascites, encephalopathy, jaundice, prolonged prothrombin time (PT), hyperbilirubinemia, and hypoalbuminemia are usual markers of impaired liver function, there is neither a standardized definition of PLF based on these markers nor precise data on their correlation with postoperative mortality. The need for a standardized definition of PLF is important for the evaluation of technical improvements in different fields of liver surgery like preoperative portal vein deprivation and the result of different methods of vascular clamping. The recent advent of liver assist devices makes it even more important to predict a poor outcome at an early stage so as to determine when they should be used.[8,9] The Child-Pugh score, which accurately evaluates preoperative liver function, is inappropriate postoperatively.[10] After surgery, encephalopathy, ascites, and hypoalbuminemia may be related to factors other than liver dysfunction itself such as the consequence of anesthesia, portal hypertension, lymphatic dissection, or hemodilution. Both bilirubin and prothrombin index (2 of the 3 components of MELD score) are frequently affected in the early postoperative days after major resection, but to which extent and at which time points have not been clearly established.[11,12]

Based on a large series of liver resections performed over a short period of time, the aim of the present study was to evaluate the reliability and usefulness of an arbitrarily defined score combining prothrombin index and bilirubin, with threshold values based upon those of Child-Pugh score (ie, 50% of normal for prothrombin index and 50 μmol/L for bilirubin) for defining PLF and assessing postoperative mortality in a population of patients undergoing hepatectomy.

METHODS

Patient Demographics

Between October 1998 and December 2002, 803 elective hepatic resections were performed at our institution and were included in a prospective database. After exclusion of patients with malignant obstructive jaundice and abnormal preoperative serum bilirubin (SB) >50 μml/L at the time of liver resection, 775 hepatectomies, performed in 704 patients were analyzed in this study. There were 383 males and 321

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TABLE 1. Indications for Hepatectomy and Operative Data in 775 Cases of Liver Resection

Indication	n (%)
Malignant diseases	531 (68.5)
Primary tumors	314 (40.5)
Hepatocellular carcinoma	233 (30.1)
Cholangiocarcinoma	51 (6.6)
Other malignancies	30 (3.9)
Secondary tumors	217 (28.0)
Colorectal metastases	163 (21.0)
Other metastases	54 (7.0)
Benign diseases	176 (22.7)
Living donors	68 (8.8)
Operative procedures	
Major hepatectomies	464 (59.9)
5 or 6 segments	120 (15.5)
3 or 4 segments	344 (44.4)
Minor hepatectomies	311 (40.1)

females with a mean age of 54 ± 10 years. Indications for resection are listed in Table 1. Malignant disease was present in 531 cases (69%), including 314 primary tumors and 217 metastases. In the remaining 244 cases without malignant disease, we included 68 patients who underwent hepatic resections for living-related transplantation (Table 1). There were 464 (60%) major hepatic resections (namely, removal of 3 segments or more) and 311 minor hepatic resections. Detailed pathologic examination of the nontumorous liver parenchyma showed that underlying changes were present in 307 cases (40%), including steatosis >30% in 107 (14%), noncirrhotic fibrosis in 237 (31%), and cirrhosis in 94 (12%).

Surgical Procedures

Selection criteria for hepatic resection included adequate medical condition of the patient and preservation of sufficient functional liver parenchyma. In addition to biologic liver function tests, preoperative imaging investigations included abdominal ultrasound and dynamic computed tomography in all patients. Additional investigations were performed when needed, according to individual situations. Portal vein embolization or ligation was performed 3 to 8 weeks before hepatectomy in 62 (8%) patients according to our protocol for preoperative portal vein occlusion: anticipated right or extended right hepatectomy in patients with chronic underlying liver disease or estimated remnant liver volume less than 30% of the total functional liver volume.[13] Liver resection was performed laparoscopically in 23 cases (3%). Conventional liver resection was performed through an exclusive abdominal incision in 729 (94%) cases, an exclusive right thoracic approach was used in 10 (1%) cases, and a thoracoabdominal approach in 13 (2%). The latter was used for bulky right-sided tumors that bulged into the pleural cavity. For major liver resection, extraparenchymal control of ipsilateral inflow and outflow was attempted before resection whenever possible. Liver transection was performed using the clamp crushing method or an ultrasonic dissector, according to the surgeon's preference. Total vascular exclusion of the liver (namely, clamping of the portal triad and the infrahepatic and suprahepatic inferior vena cava) was used in 34 cases (4.4%). Other resections were performed under intermittent portal triad clamping in 507 (65%) cases for a mean duration of 48 ± 23 minutes. In 234 (30%) cases, liver resection was performed without hepatic inflow occlusion.

Postoperative Course

Admission in Intensive Care Unit (ICU) was routine in patients with cirrhosis or associated cardiovascular comorbidities, in those who were submitted to extensive hepatectomies, or in case of intraoperative adverse event (such as hypothermia or massive bleeding). Our policy was to avoid the use of postoperative fresh frozen plasma. As a result, no patient included in this series received fresh frozen plasma or any other substitutive to coagulation factors during the first postoperative week. The aim of this study was to investigate if the early kinetics of liver function tests correlated with the postoperative outcome. For this purpose, liver function tests were sampled routinely on postoperative days (POD) 1, 3, 5, and 7 and complications were recorded prospectively. Based on the Child-Pugh score, threshold values of 50% for PT and of 50 μmol/L for SB were chosen to evaluate the impact of these tests on postoperative mortality. The arbitrary choice of these threshold values was justified by the fact that they correspond to the widely used limits of Child score.

The principal endpoint was postoperative mortality, defined as death occurring during postoperative in hospital stay or within 60 days of surgery. Postoperative complications were divided into major and minor. Minor complications were the adverse events with no or minimal impact on in-hospital stay. Life-threatening complications were considered as major postoperative complications. Complications with a clear link with liver failure included portal vein thrombosis, infected ascites, severe sepsis, renal failure, and gastrointestinal hemorrhage.

Statistical Methods

Statistical analysis was performed using Epi Info version 2002 (Centers for Disease Control and Prevention). Data are expressed as median values and ranges or absolute values and percentages. P values <0.05 were considered significant. Survival was analyzed using the Kaplan-Meier estimates and comparisons were performed using the log-rank test. Student t test, χ^2 test, and Fisher exact test were used for univariate analysis where needed. Multivariate analysis was performed using logistic regression. Odds ratio with 95% confidence intervals derived from logistic regression were calculated. Sensitivity and specificity, as well as test accuracy, were computed for the proposed criteria of PLF.

RESULTS

Kinetics of Postoperative Liver Function Tests

The kinetics of postoperative PT and SB are shown in Figure 1. Postoperative PT level was minimum on POD 1 (65% ± 18%) and, thereafter increased progressively reaching a level similar to preoperative values on POD 5 (83% ± 19% versus 95% ± 13%). Postoperative SB increased until

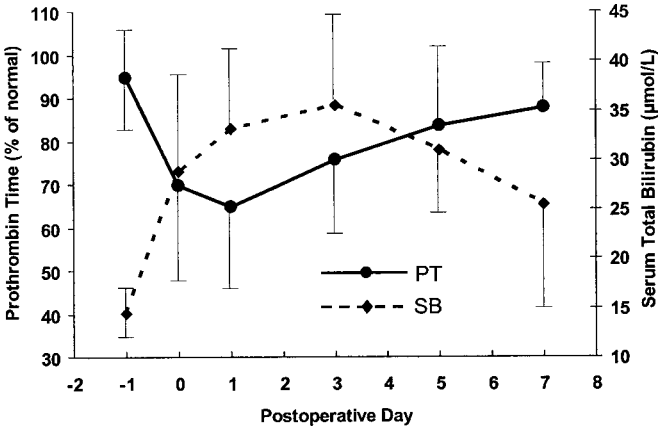

FIGURE 1. Kinetics of postoperative biologic liver function tests. Means and SD of prothrombin time (PT) and total serum bilirubin (SB) in overall group of hepatectomies. Kinetic of postoperative prothrombin time (PT) and serum total bilirubin level (SB).

POD 3 (36 ± 29 μmol/L) and thereafter slowly decreased to 26 ± 11 μmol/L on POD 7. The trend of these 2 biologic markers to return to preoperative values was evident on POD 5.

Operative Mortality and Impact of PT <50% and/or SB >50 μmol/L

In-hospital death occurred in 26 patients (3.4%), including 21 (80%) with abnormal liver parenchyma (12 of them with cirrhosis) and 20 (77%) following major hepatectomies. Three patients died early after major resection: 1 patient of myocardial infarction on POD 2 and 2 of peritonitis following bowel necrosis on POD 3 and POD 5, respectively. Apart from these 3 patients who obviously died without liver dysfunction, the 23 other patients died between POD 5 and 39 (median POD 15) from multiple complications. These complications were first identified between POD 3 and 18 (median, 10). Except for the 3 early deaths, the remaining 23 deaths were due to postoperative complications clearly related to liver dysfunction, including portal vein thrombosis in 7, bacterial peritonitis in 6, severe sepsis in 16, renal failure in 5, and gastrointestinal hemorrhage in 2.

The mortality rate increased from 16% to 40% in patients who had PT <50% on POD 3 and POD 7, respectively. In parallel, the mortality rate increased from 11% to 17% in patients with SB >50 μmol/L on POD 3 and POD 7, respectively (Table 2).

Whatever the postoperative time point, patients with neither PT <50% nor SB >50 μmol/L at any time during the study period had a significantly lower risk of mortality, around 1%, compared with the remaining patients with either PT <50% or SB >50 μmol/L (P <0.001). As shown in Table 2, the prediction of a fatal outcome was even more accurate when both variables were used in combination. Seven percent and 2.5% had simultaneously PT <50% and SB >50 μmol/L on POD 3 and POD 7, respectively. Mortality was 19% in those with PT <50% and SB >50 μmol/L on POD 3 compared with 63% on POD 7. We empirically defined the "50-50 criteria" as the concomitant presence of PT <50% and SB >50 μmol/L. On POD 5, patients who met this criterion had a 59% risk of early postoperative mortality, compared with 1.2% risk of mortality if the criteria was not fulfilled (P <0.001). The relative risk of death was 66 (95% CI, 30–147) if the 50-50 criteria was present on POD 5 and the accuracy of this test to predict in-hospital mortality was 97.7% (95% CI, 96.6%–98.7%; sensitivity, 69.6%; specificity, 98.5%).

TABLE 2. Operative Mortality According to Occurrence of Prothrombin Time <50% and/or Serum Bilirubin <50 μmol/L

	POD1	POD3	POD5	POD7
PT				
PT >50%	1.5%	1.3%	1.5%	1%
PT <50%	10%	16%	33%	40%
SB				
SB <50 μmol/L	2.7%	1.9%	1.1%	1.5%
SB >50 μmol/L	7%	11%	15%	17%
"50-50 criteria"				
PT >50% *and* SB <50 μmol/L	1.3%	0.8%	1.2%	0.6%
PT <50% *and* SB >50 μmol/L	14%	19%	59%	63%

POD indicates postoperative day; PT, prothrombin ratio; SB, serum total bilirubin level.

A total of 172 (22%) patients stayed more than 48 hours in ICU, with a mean duration of 8.4 ± 7.2 days, ranging from 3 to 60 days. All of the 11 patients who survived, despite fulfilling the 50-50 criteria on POD 5, experienced severe complications with a mean stay in ICU of 22 ± 11 days (range, 4–57 days) and a mean hospital stay of 43 ± 8 days (range, 17–69 days). The 7 postoperative deaths without the 50-50 criteria on POD 5 occurred between POD 10 and POD 60 and were due to gastrointestinal hemorrhage secondary to portal vein thrombosis in 3 and severe sepsis in 4. The 50-50 criteria was included in a multivariate logistic regression model with other variables. As shown in Table 3, the 50-50 criteria on POD 5, age over 65 years, and the presence of severe fibrosis on nontumorous liver parenchyma were the only independent predictors of death on multivariate analysis, including variables otherwise significant on univariate analysis (namely, extension of liver resection [major or minor hepatectomy], malignant disease, presence of steatosis of more than 30% and the need for peroperative blood transfusions).

DISCUSSION

Technical improvements in the field of liver surgery have increased the possibility to extend the volume of resected parenchyma, leaving a small remnant liver. It also made it possible to perform resections in patients with underlying liver lesions such as fibrosis, cirrhosis, severe steatosis, and/or chemotherapy-related liver lesions.[1–6] All these factors potentially impair postoperative regeneration and favor the occurrence of PLF.[1,2,7] The presence of PLF, by turn, increases the patient's susceptibility to major complications, especially severe infections, which often result in early postoperative death.[14,15] Although this particular condition is of

TABLE 3. Predictive Factors of Operative Mortality After Liver Resection

	Univariate Analysis		Multivariate Analysis	
Prognostic Factors	**Odds Ratio (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***
Age >65 yr	1.8 (0.78–4.19)	0.17	4.83 (1.24–18.85)	0.023
Major hepatectomy	1.9 (0.75–4.95)	0.198	—	—
Malignancy	—*	<0.001	—	—
Steatosis >30%	0.9 (0.28–3.32)	1.0	—	—
Fibrosis F3 or F4	5.7 (2.42–13.4)	<0.001	4.31 (1.38–13.49)	0.012
"50-50 criteria"	136.5 (46.8–397.7)	<0.001	215.6 (54.1–860.7)	<0.001
Preoperative blood transfusions	2.3 (0.99–5.46)	0.07	—	—

*No odds ratios were calculated because all death occurred in patients with malignancies.

increasing frequency, a standardized definition of PLF is still lacking. None of the previously proposed definitions of liver failure established outside the context of surgery can be easily extrapolated to the early period following liver resection. Some of the variables used to assess liver function, namely, alanine aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase, are influenced by the surgical insult to and/or regeneration of the remnant liver rather than reflecting hepatic function.[11,12] Child-Pugh score, which was designed to predict the postoperative outcome of cirrhotic patients, is likely to be biased in the postoperative period.[10,16] Neurologic status and ascites are not useful prognostic factors in the early postoperative course. Neurologic status, indeed, can be affected by external factors such as anesthesia and the administration of sedative drugs. Similarly, ascites, which can be related to the extent of resection and/or to lymph nodes dissection, is not a reliable marker of hepatic dysfunction.[17] Serum albumin, a protein with a long half-life, can also be affected by nonspecific factors such as preoperative nutritional status, postoperative ascites, and hemodilution.[18]

In contrast to the variables cited above, 2 components of Child-Pugh score, namely, PT and SB, are less likely to be biased following liver resection and have indeed been used by others in the evaluation of liver function in a similar clinical setting.[1–3,8,19] However, the threshold values and the time point at which these 2 biologic factors are accurate indicators of PLF have not been determined. Five large studies evaluating the results of liver resections after the year 2000 have arbitrarily used different limits for PT (range, 30%–70%) and SB (range, 50–85 μmol/L) at different postoperative time points.[1–3,8,19,20] Additionally, the fact that liver function tests follow a specific kinetic after liver resection, characterized by early impairment and subsequent normalization, has not been taken into account.

The results of the present study clearly confirm that following the early physiologic changes in these 2 variables (from POD 1 to POD 3): there is a trend to a return to normal values on POD 5. Our approach was therefore to analyze the accuracy of PT <50% and SB >50 μmol/L at different time points for predicting postresection outcome. The values of PT and SB indicating a significant impairment of liver function were chosen according to the widely used Child score. The value of 50% of normal for PT corresponds to an INR of 1.7, and a serum bilirubin of 50 μmol/L corresponds to a value of 3 mg/dL. Again, early alterations of liver function tests following hepatic resection do not always reflect clinically relevant events. The results of this study showed that, during the first 3 postoperative days, both PT <50% or a SB >50 μmol/L did not accurately predict outcome. On the contrary, the persistence of either PT <50% or SB >50 μmol/L on POD 5 proved important for predicting mortality and might be considered an indicator of PLF. The main result of this study was to demonstrate that the conjunction of these 2 values on POD 5, the 50-50 criteria, could predict nearly 100% morbidity rate and 50% mortality rate.

The main preoperative factors predicting postoperative liver dysfunction include the presence of impaired preoperative liver function, the presence of chronic liver disease, extensive liver resection, and the presence of a small remnant liver.[2,5,21–24] Although the aim of the present study was not to identify preoperative predictive factors of PLF, the presence of a large proportion of patients at risk allowed us to observe a substantial number of adverse events associated with or directly related to liver failure. Consequently, the overall mortality rate of 3.4% in this population of patients, including a large number of major resections with abnormal underlying liver parenchyma, is far from the zero mortality achieved in highly selected groups.[2,25]

As shown in the present study, more than 50% of the postoperative deaths occurred after 2 weeks. Indeed, unlike the rapid evolution of patients with fulminant hepatic failure, PLF occurring after liver resection is associated with more insidious complications that are more difficult to diagnose. The early recognition of PLF, which precedes clinical evidence of complications, was one of the key findings of this study. Before POD 3, early impairment of liver function tests had a poor predictive value. The presence of 50-50 criteria after POD 3, in contrast, should be considered as an alarm. The presence of 50-50 criteria on POD 5, in particular, requires aggressive investigations in search of specific complications. These aggressive investigations may include multiple bacteriologic examinations to identify bacterial peritonitis or pneumonia as well as Doppler-US and CT scans to rule out portal thrombosis. These 2 complications inevitably lead to death if not identified and treated promptly. The presence of 50-50 criteria on POD 5 may also help to decide the use of liver assist devices or even to consider rescue liver transplantation in selective cases.

A number of studies have laid down preoperative criteria to select patients for hepatectomy, while others have defined the preoperative and intraoperative interventions to increase the safety of resections.[1–5] The present study is the first to propose a tool that can be used in the postoperative period to accurately predict outcome, leading to a comprehensive definition of PLF. We think that there is a strong need for standardization of the definition of PLF to evaluate the results of innovations in the different fields of liver surgery, including the effect of preoperative portal vein deprivation and the impact of different techniques of vascular clamping. We have shown that the 50-50 criteria on POD 5 is an accurate and early indicator of PLF, predicting 50% mortality after liver resection. Although the results of this study require a prospective validation using our 50-50 criteria and the investigation of the applicability of MELD score, we propose to define postoperative PLF as the presence of 50-50 criteria on POD 5.

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Discussions

DR. SLOOFF: It is a privilege for me to comment on this paper from such a distinguished Hepatobiliary Unit.

The paper concerns a proposal for a standardized definition for liver failure after hepatectomy. The incentive, as the authors state, for such a definition is its need for comparison of different resection techniques or for the initiation and evaluation of experimental or clinical extracorporeal liver support systems.

The arguments for the choice of the 2 variables from the definition, prothrombin time and serum total bilirubin is arbitrary and thus debatable. It is based on the fact that they are part of the Child-Pugh and MELD scores originally not validated for post resection functional evaluations.

Also, the cutoff points for PT and serum bilirubin are taken arbitrarily, and this counts also for identifying day 5 as the time point for the kinetics. Looking at Figure 1, the trend of normalization of the PT values is already present from day 1 onwards and for serum total bilirubin on day 4. I question as well if these kinetics depicted in this figure are really the same for patients with cirrhosis, fibrosis normal liver tissue containing tumors, or healthy living donors.

It is conceivable, especially in this very heterogeneous patient material with the varying resection techniques, that other variables related to the patients and the type and techniques of the operations were also related to postoperative liver failure and mortality.

Why was not first a multivariate analysis performed taking mortality due to liver failure as the major endpoint? If dynamic factors were predictive, the next step could have been the analysis of the kinetics.

I thank the authors for sending the paper beforehand and giving me the opportunity to study their analysis.

DR. BELGHITI: Thank you for this very interesting comment and the point you made. As you said, we need a uniform definition for postoperative liver failure. The inaccuracy of clinical assessment during the postoperative period prompts the use of biologic factors. Why we selected prothrombin time less than 50% and serum bilirubin more than 50 μmol/L (50-50 criteria) at day 5?

Prothrombin time and bilirubin were chosen as these factors are included in both Child and MELD scores and are the most significant factors indicating liver function. Second, the level of PT <50% corresponding to INR of 1.7 and bilirubin >50 μmol/L corresponding to 3 mg/dL indicate significant impairment of liver function in the Child-Pugh score. Third, the day 5 was considered because these 2 tests should return to normal values by this time. Before POD 3, early impairment of liver function test has a poor predictive value; the persistence of 50-50 criteria after POD 3 should be considered as a red signal with a risk of 20% mortality, which increases to 60% at day 5.

Although we analyzed a large group of patients in a short period of time, I agree that this group was heterogeneous. Therefore, we add a multivariate analysis demonstrating that the most significant predictive factor of mortality was the presence of 50-50 criteria at day 5.

DR. RIKKERS: Prof. Belghiti, this is a very nice contribution.

Both of the variables that you analyzed can be affected by blood transfusion. Were these 2 factors predictive independent of whether patients were transfused or not during their operations?

DR. BELGHITI: I agree that you have an important point. Perioperative blood transfusion did not reach significance level even on univariate analysis. Our policy is to avoid the use of postoperative fresh-frozen plasma. In order not to interfere with the postoperative coagulation tests, no patient included in this study received fresh frozen plasma during the first postoperative week.

DR. CLAVIEN: I would like to congratulate the authors for this important study including a large population of patients, and very importantly, using a database covering a relatively short period of time. The credibility and applicability of the data are also boosted by the selection of readily available and objective criteria to the clinicians. Complicated formulas are typically unpopular and felt out of clinical practice rapidly. I have 2 questions. First, why did you limit your data to postoperative day 5? Did you perform any types of multivariate analyses, for example, with an attempt to identify earlier criteria including intraoperative events? On the same token, a significant proportion of cirrhotic patients were included? Is cirrhosis per se a risk factor, and should we not consider a specific formula for this high-risk population? My second question relates to the validation of such prognostic score coming from a database. Did you or do you plan to apply this score system in your next 100 or 200 patients to prospectively test the actual value of your 50-50 criteria?

DR. BELGHITI: Thank you for this excellent question. Although I did not show this result in my slides, the presence of chronic liver disease is an important impact factor on postoperative mortality and the presence of 50-50 criteria at day 5 has a higher predictive value for risk of mortality than in patients with normal liver. From the methodologic point of view, this criterion should be validated prospectively, and we are currently doing so. However, since the result of this study, we have dramatically changed our postoperative approach toward our patients with this 50-50 criterion. On day 5, the presence of this criterion leads us to conduct a multidisciplinary meeting, aggressive investigations including multiple bacteriological examinations to identify ascites and pneumonia as well as Doppler ultrasound and CT scan to rule out portal thrombosis. These 2 complications inevitably lead to death if not treated promptly. Therefore, it is probably unethical for a randomized study to be conducted on them.

DR. HÖCKERSTEDT: This 50-50 criterion is a very nice expression, of course, but how useful is this knowledge? Because on day 5, it is too late to do much for the individual patients. The ICU people can keep them alive for a few days or weeks but, as you say yourself, 60% of them will die eventually. In that respect, I am afraid that it is not of much use. Certainly, we need the preoperative tests, but now we are talking about surprises happening to the patients during or after surgery. And on day 5, it is too late to improve the situation, so I suggest we concentrate on day 1 or perhaps day 2.

DR. BELGHITI: I feel that you are too pessimistic. The presence of a low PT on day 1 is not a grave sign. The postoperative bilirubin value, which is an important factor of liver impairment, is exceptionally elevated on day 1. Therefore, before day 3, it is quite impossible to define biologic postoperative liver failure. It is on day 5 that both PT and bilirubin should return to normal value; their levels around 50-50 is a sign of liver failure and have a high predictive value of postoperative death. Although it is always too late, we must keep in mind that the majority of postoperative deaths occur after 2 weeks, leaving some place for searching and treating complications. Furthermore, it seems difficult to decide on the use of liver assist devices or even to consider rescue liver transplantation in selective cases before POD 5.

DR. HÖCKERSTEDT: We do not need slow reactors like bilirubin, but fast reactors that have a half time, which is just a few hours.