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# Risk of Major Liver Resection in Patients With Underlying Chronic Liver Disease

## A Reappraisal

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**Objective**
To explore the relation of patient age, status of liver parenchyma, presence of markers of active hepatitis, and blood loss to subsequent death and complications in patients undergoing a similar major hepatectomy for the same disease using a standardized technique.

**Summary Background Data**
Major liver resection carries a high risk of postoperative liver failure in patients with chronic liver disease. However, this underlying liver disease may comprise a wide range of pathologic changes that have, in the past, not been well defined.

**Methods**
The nontumorous liver of 55 patients undergoing a right hepatectomy for hepatocellular carcinoma was classified according to a semiquantitative grading of fibrosis. The authors analyzed the influence of this pathologic feature and of other preoperative variables on the risk of postoperative death and complications.

**Results**
Serum bilirubin and prothrombin time increased on postoperative day 1, and their speed of recovery was influenced by the severity of fibrosis. Incidence of death from liver failure was 32% in patients with grade 4 fibrosis (cirrhosis) and 0% in patients with grade 0 to 3 fibrosis. The preoperative serum aspartate transaminase (ASAT) level ranged from 68 to 207 IU/l in patients with cirrhosis who died, compared with 20 to 62 in patients with cirrhosis who survived.

**Conclusion**
A major liver resection such as a right hepatectomy may be safely performed in patients with underlying liver disease, provided no additional risk factors are present. Patients with a preoperative increase in ASAT should undergo a liver biopsy to rule out the presence of grade 4 fibrosis, which should contraindicate this resection.

Although the technique of liver resection has improved considerably during the past 10 years,[1,2] major liver resections continue to carry a high risk in patients with underlying liver disease, in particular cirrhosis,[3] because of the high incidence of postoperative liver failure. Major liver resections are therefore seldom performed in patients with Child grade A cirrhosis; even a minor hepatectomy is poorly withstood by patients with grade B or C cirrhosis.

Hepatocellular carcinoma is by far the most frequent indication for liver resection in patients with a chronic liver disease, because cirrhosis is the predominant risk factor for the development of this tumor. However, because infection with hepatitis B (HBV) or C (HCV) virus is an independent risk factor for the development of hepatocarcinogenesis and is present in >80% of patients with hepatocellular cancer,[4] the range of pathologic changes in the nontumorous liver is in fact much wider than previously thought, ranging from simple fibrosis to severe cirrhosis.[5]

Surgical series assessing the perioperative risk associated with liver resection have not accurately taken into account this range of pathologic changes. The nontumorous liver is usually stratified as either cirrhotic or normal,[6] and the cirrhotic group may therefore include a variable proportion of patients with less severe histologic changes. This may explain the differences in inpatient mortality rates after major liver resection in "cirrhotic" patients, ranging from 3%[7] to 48%.[8] For the same reason, the recent claims[7,9,10]

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**Table 1. CHARACTERISTICS OF PATIENTS ACCORDING TO FIBROTIC CHANGES IN NONTUMOROUS LIVER**

| Variables | Grade 0 (normal) | Grade 1 | Grade 3 | Grade 4 (cirrhosis) |
|---|---|---|---|---|
| No. of patients | 8 | 14 | 13 | 20 |
| Age (mean ± SD, years) | 40 ± 17 | 54 ± 15 | 61 ± 9 | 58 ± 12 |
| Preopoperative transarterial chemoembolization | 25% | 21% | 38% | 15% |
| Tumor diameter (mean, cm) | 10 ± 5 | 10 ± 4 | 9 ± 3 | 8 ± 4 |
| Weight of specimen (mean, g) | 1331 ± 650 | 1310 ± 470 | 1100 ± 320 | 1150 ± 430 |
| Duration of clamping (mean, min) | 42 ± 12 | 34 ± 10 | 31 ± 9 | 34 ± 11 |
| HBV positive markers* | 1/8 | 6/14 | 5/13 | 10/19 |
| Anti-HCV positive ve* | 0/7 | 1/8 | 1/7 | 4/14 |
| Preoperative ASAT (median, range) | 29 (21–120) | 44 (14–240) | 45 (14–360) | 45 (20–210) |

* In patients with grade 3 or 4 fibrosis without positive serologic markers of HBV or HCV infection, the cause of the underlying liver disease was chronic alcohol ingestion (three patients in grade 3 and four patients in grade 4) and hemochromatosis (three patients in grade 3 and two patients in grade 4).

that major liver resections may be safely performed in patients with cirrhosis require a more precise evaluation.

In an effort to address this issue, we analyzed the postoperative course of 55 patients undergoing the same extensive resection (right hepatectomy) for the same indication (hepatocellular cancer) as a function of the semiquantitative histologic grading of the underlying liver disease and of other preoperative variables.

## PATIENTS AND METHODS

Between 1985 and 1996, curative resection of hepatocellular cancer was performed in 257 patients. Of these, 55 patients who had undergone a formal right hepatectomy (Couinaud's segments 5, 6, 7, and 8) without preoperative biliary drainage (none of these patients had a significant compression of the segmental biliary ducts) or portal vein embolization were selected for analysis. All patients with chronic liver disease had normal liver function as assessed by the Pugh-Child classification (grade A). Serologic markers of HBV and HCV infection were present in 22/54 (41%) and 6/38 (16%) of the tested patients, respectively.

Liver sections sampled from the pathologic specimen distant from the tumor were retrospectively reviewed by one senior pathologist (JFF), and the presence of fibrosis in the underlying liver was graded from 0 to 4 according to the classification of Knodell et al.[11] Accordingly, 8 (14%) patients had a normal liver without fibrosis (grade 0), 14 (25%) had fibrous portal expansion (grade 1), 13 (24%) had bridging fibrosis (grade 3), and 20 (36%) had cirrhosis (grade 4). Piecemeal necrosis (without bridging necrosis), intralobular degeneration and focal necrosis, and portal inflammation were present in 23 (42%), 13 (24%), and 48 patients (87%), respectively.

Liver resections were performed in a standardized fashion.[12] An abdominal incision was used in all patients. Right-sided pedicular vascular structures were ligated and transected, after which the right lobe was mobilized from the anterior vena cava, with division of all accessory hepatic veins. The right hepatic vein was isolated extraparenchymally and divided. The dissection plane was established after demarcation by devascularization. Parenchymal transection was performed under inflow occlusion in all patients except two with cirrhosis using a Kelly forceps and ultrasonic dissector. The tumor-free margins were checked repeatedly using intraoperative ultrasonography. Biliary and vascular radicles were secured by sutures and clips, and liver cut surface was sealed using fibrin glue (LFB, 91958 Les Vlis, France).

Liver function tests were recorded on postoperative days 1, 3, 5, 7, and 10. Postoperative ascites was treated with diuretics, sodium restriction, albumin perfusion, and an ascitic tap as required. Routine abdominal ultrasound was carried out between postoperative days 3 and 6, or in any patient with a suspected infected collection. All fluid collections were drained percutaneously with bacteriologic cultures. Pulmonary complications were defined as pneumonia or pleural effusion. The mean length of hospital stay was recorded.

Comparison of frequencies was performed using the chi square test or the Fisher's exact test. Comparison between postoperative liver function tests was performed using the Student's t test, the Kruskal-Wallis analysis of variance by ranks, or the median test. Multivariate analysis was performed using logistic regression and discriminant analysis.

## RESULTS

The characteristics of the patients according to the semiquantitative grading of fibrosis in the nontumorous liver are summarized in Table 1. The size of the tumor, the weight of the resected specimen, and the duration of clamping were comparable in the four groups, suggesting that these patients had indeed undergone the same extensive resection using the same technique. The proportion of patients requir-

**Table 2. UNIVARIATE ANALYSIS OF RISK OF DEATH FROM LIVER FAILURE AMONG 19 PATIENTS WITH GRADE 4 FIBROSIS (CIRRHOSIS) UNDERGOING RIGHT HEPATECTOMY FOR HEPATOCELLULAR CANCER**

| Variables | | No. of Patients at Risk | No. of Patients Dying of Liver Failure | p (Fisher's exact test) |
|---|---|---|---|---|
| Age (years) | <60 | 10 | 0 | <60 *vs.* >60 |
| | 60–65 | 4 | 3 | 0.003 |
| | >65 | 5 | 3 | |
| Preoperative ASAT | <1N* | 7 | 0 | <2N *vs.* >2N |
| | 1–2 N | 7 | 1 | 0.0005 |
| | >2N | 5 | 5 | |
| Preoperative ALAT | <1N | 10 | 0 | <2N *vs.* >2N |
| | 1–2N | 6 | 3 | 0.02 |
| | >2N | 3 | 3 | |
| Esophageal varices | Present | 10 | 2 | NS |
| | Absent | 7 | 3 | |
| Transfusion (no. units packed red cells) | 0 | 7 | 1 | <5 *vs.* >5 |
| | 1–5 | 7 | 1 | 0.01 |
| | 6–10 | 2 | 1 | |
| | >10 | 3 | 3 | |

ALAT = alanine transaminase; ASAT = aspartate transaminase; NS = not significant.
One patient who died of cardiac failure on postoperative day 1 was excluded from analysis.
* N, normal upper range

ing an intraoperative transfusion (overall 49%) was similarly not significantly different between the four groups.

## Inpatient Deaths

Nine patients died in the postoperative period (16.3%), six of liver failure and three of other causes (myocardial infarction, acute cardiac failure, and perforated gastroduodenal ulcer associated with thrombosis of the hepatic artery). Death from liver failure was associated with sepsis or variceal bleeding and occurred in a delayed fashion between postoperative days 11 and 45. Only grade 4 fibrosis (cirrhosis) was a significant independent variable. The incidence of death from liver failure was 32% in patients with grade 4 fibrosis, compared with 0% in patients with less severe or no fibrosis ($p = 0.001$).

In patients with grade 4 fibrosis, age older than 60 years and a preoperative increase in serum aspartate transaminase (ASAT) more than twice the normal upper range (2N) were associated with a significant increase in death from liver failure (Table 2). All six patients were older than 60 years and had increased preoperative serum ASAT levels (range 68 to 207 IU/l vs. 20 to 62 IU/l in those who survived surgery). In addition, cirrhotic patients who died were more likely to have experienced massive intraoperative bleeding. Other variables tested were comparable in cirrhotic patients who did or did not develop fatal liver failure, in particular the weight of the resected specimen (1248 ± 456 g *vs.* 1097 ± 433 g) and the duration of clamping (36 ± 8 minutes *vs.* 32 ± 13 minutes). Piecemeal necrosis and portal inflammation were not independent variables when tested along with the preoperative increase in ASAT > 2N.

## Postoperative Complications

The incidence of postoperative complications in the entire group was 70%. The most frequent complications were ascites (56%), lung infection or pleural effusion (38%), transient encephalopathy (20%), kidney failure (13%), portal vein thrombosis (7%), and upper gastrointestinal bleeding (4%). Risk factors for the most frequent of these complications are summarized in Table 3. By multivariate analysis, the risk of ascites was significantly correlated with the intensity of fibrosis, the risk of pulmonary complications and encephalopathy with the volume of intraoperative transfusions, and the risk of kidney failure with preoperative serum ASAT level > 2N. Ascites and the severity of fibrosis were therefore the only postoperative complications and characteristics of the nontumorous liver that were correlated.

In patients with grade 4 fibrosis, preoperative ASAT level > 2N was associated with a greater incidence of kidney failure (4/5 *vs.* 0/14, $p = 0.001$) and encephalopathy (5/5 *vs.* 2/14, $p = 0.001$). Age older than 60 years had a comparable although less significant influence on the incidence of kidney failure ($p = 0.03$) and encephalopathy ($p = 0.01$). Other pathologic variables did not independently increase the postoperative morbidity rate in these patients with cirrhosis.

## Postoperative Kinetics of Liver Function Tests

Because the development of a fatal postoperative complication probably affects the results of liver function tests, we first analyzed the kinetics of the prothrombin time and bilirubin in patients who survived surgery. Right hepatectomies were associated on postoperative day 1 with a decrease of prothrombin time to 48 ± 10%. This value was not influenced by any of the pathologic features of the underlying liver disease, nor by the age of the patient, preoperative liver function test results, amount of intraoperative blood transfusion, or duration of clamping of the hepatic pedicle. Thereafter, the prothrombin time tended to return to normal values. The speed of recovery was influenced by the severity of the underlying fibrosis (Fig. 1A): it was significantly delayed during the first postoperative week in patients with grade 3 fibrosis and during several weeks in patients with grade 4 fibrosis. Comparable results were observed for serum bilirubin: levels increased early after

**Table 3. RISK OF POSTOPERATIVE ASCITES, LUNG COMPLICATIONS, ENCEPHALOPATHY, AND KIDNEY FAILURE IN 53 PATIENTS UNDERGOING RIGHT HEPATECTOMY FOR HEPATOCELLULAR CANCER**

| Variables | | Ascites (%) | p | Lung (%) | p | PSE (%) | p | Kidney (%) | p |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | <60 | 48 | 0.2 | 41 | 0.6 | 11 | 0.07 | 4 | 0.03 |
| | >60 | 65 | | 35 | | 31 | † | 23 | † |
| Preoperative ASAT | ≤2N | 58 | 0.6 | 34 | 0.3 | 15 | 0.04 | 7 | 0.02 |
| | >2N | 50 | | 50 | | 42 | † | 33 | |
| Preoperative ALAT | ≤2N | 56 | 0.8 | 40 | 0.6 | 19 | 0.4 | 9 | 0.08 |
| | >2N | 60 | | 30 | | 30 | | 30 | |
| Esophageal varices | Absent | 51 | 0.2 | 41 | 0.5 | 15 | 0.2 | 10 | 0.3 |
| | Present | 70 | | 30 | | 30 | | 20 | |
| Fibrosis score | 0–1 | 36 | 0.01 | 27 | 0.1 | 9 | | 4 | 0.4 |
| | 3 | 66 | | 33 | | 17 | † | 17 | |
| | 4 | 73 | | 52 | | 37 | 0.03 | 21 | |
| Transfusion (No. units packed red cells) | 0 | 52 | 0.2 | 26 | 0.07 | 18 | 0.001 | 11 | 0.4 |
| | 1–5 | 53 | | 42 | | 5 | | 11 | |
| | >5 | 85 | | 71 | | 71 | | 29 | |

Two patients who died on postoperative day 1 of heart failure were excluded from analysis.
ALAT = alanine transaminase; ASAT = aspartate transaminase; N = normal upper range; PSE = encephalopathy.
† Not significant by multivariate analysis

surgery and progressively returned to normal thereafter. The magnitude of early hyperbilirubinemia was not influenced by any of the variables tested. The speed of recovery was influenced by the severity of the underlying fibrosis: it was significantly delayed during the first postoperative week in patients with grade 3 and 4 fibrosis compared with patients without fibrosis (see Fig. 1B).

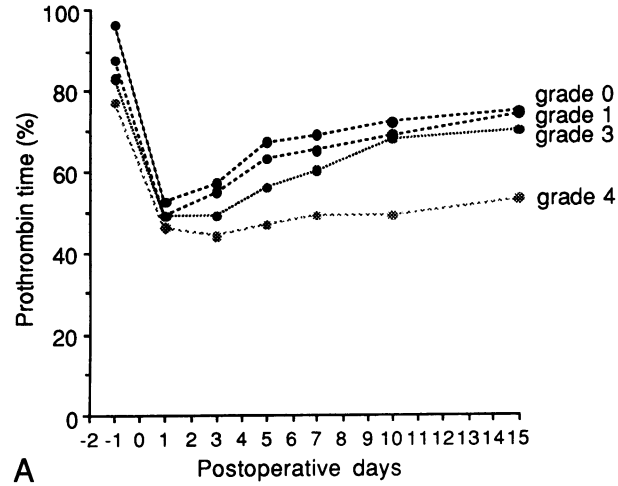
Hence, the magnitude of fibrosis significantly delayed the recovery of liver function tests beyond postoperative day 15, at which time some of these patients started to die of liver failure. Because age and preoperative increase in ASAT were preoperative prognostic factors for the risk of death from liver failure in patients with grade 4 fibrosis (cirrhosis), we next investigated how these variables influenced the postoperative kinetics of liver function tests (Fig. 2). In patients with an ASAT level > 2N (all of whom died of liver failure), prothrombin time and serum bilirubin levels further deteriorated. The difference was significant as early as postoperative day 3 (range of bilirubin 40 to 102 IU/l in survivors *vs.* 102 to 228 IU/l in those who died of liver failure).

## DISCUSSION

This is to our knowledge the first study investigating in detail the risk of a major hepatectomy as a function of a semiquantitative assessment of the predominant pathologic features present in the nontumorous liver. We have shown that fibrosis is the pathologic feature with the most influence on outcome and that the severity of fibrosis is correlated with the risk of postoperative ascites and the duration of postoperative liver failure, but that death from liver failure is observed only in patients with grade 4 fibrosis (cirrhosis) who have additional risk factors—in particular, preoperative ASAT level > 2N.

The inpatient mortality rate after major hepatectomies performed by experienced surgeons in patients with cirrhosis may be as low as 3%[7] or as high as 48%.[8] The discrepancy between these experiences may result from a difference in the extent of resection, the definition of cirrhosis and assessment of hepatic function, or the presence of additional risk factors. To rule out the influence of some of these variables, our analysis was performed in a population of patients undergoing the same resection using a standardized technique. In addition, all our patients were Pugh-Child grade A. It may be argued that a better assessment of liver function would have been achieved with more sophisticated tests, in particular the indocyanine green (ICG) retention rate. However, whereas some studies have shown that this test was more accurate than conventional tests to predict postoperative death after hepatectomy, there is no consensus yet on the dividing line that best predicts outcome,[9,13,14] nor on its accuracy.[9,13,15] In addition, the range of ICG retention rate is identical among patients with cirrhosis or a less severe degree of chronic liver injury who undergo resection.[9] We therefore relied primarily on the histology of the nontumorous liver and on the presence of additional risk factors to assess the risk of liver resection.

Fibrosis was the pathologic variable that best correlated with outcome; lobular necrosis had no influence, and piecemeal necrosis or portal inflammation had only a marginal influence. The presence of fibrosis increased both the duration of postoperative liver failure and the incidence of ascites. The correlation between fibrosis and ascites is not



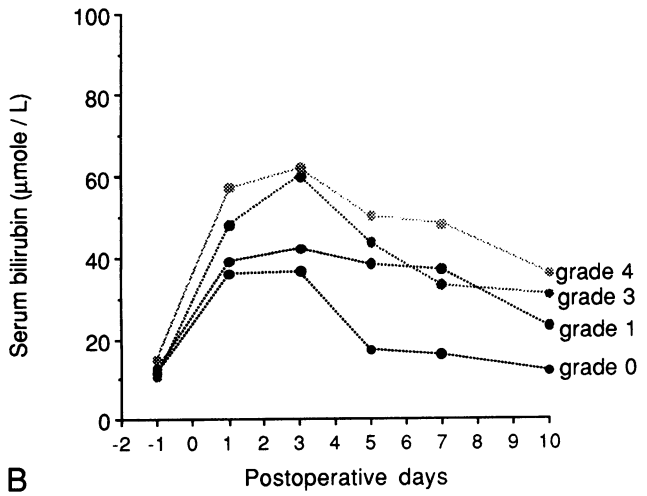
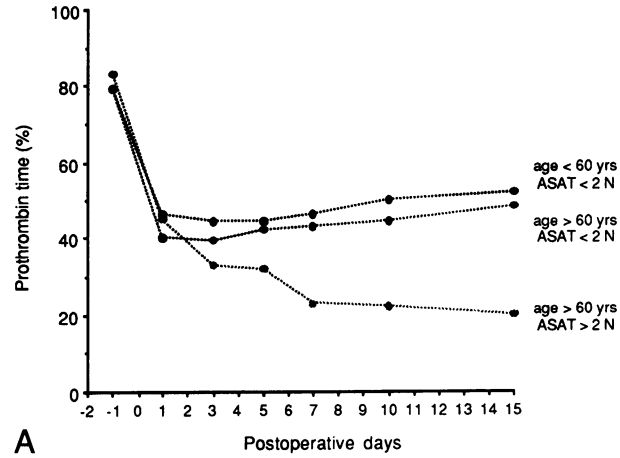




**Figure 1.** Postoperative kinetics of median prothrombin time (A) and serum bilirubin (B) after a right hepatectomy for hepatocellular cancer as a function of the fibrosis grade of the nontumorous liver. Grade 0 = 8 patients, grade 1 = 13 patients, grade 3 = 12 patients, grade 4 = 13 patients. The nine patients who died after surgery were excluded from analysis.

surprising, although it is worth underlining that its incidence was still 36% in patients with grade 0 or 1 fibrosis. This high incidence in patients without significant underlying liver disease has previously been reported[9] and suggests that the mechanism of ascites after liver resection is multifactorial. A more interesting observation was that the severity of fibrosis correlated with the duration of postoperative liver failure, whereas its severity on postoperative day 1 was not influenced by the underlying liver disease. This delayed recovery in patients with fibrosis may be related to the so-called impaired functional reserve or to a delayed regeneration of the remnant liver.

Our data, however, suggest that this impaired recovery was not necessarily associated with an increased risk of death from liver failure, provided the patient had no additional risk factors, such as age or a preoperative increase in ASAT. The inpatient mortality rate was 0% in the 10 patients with cirrhosis who were younger than 60 years but rose to 100% in patients with cirrhosis and a preoperative ASAT level > 2N. This influence of preoperative cytolysis confirms a previous work from our institution.[16]

In patients with cirrhosis, a preoperative increase in ASAT > 2N was associated with an increased risk of intraoperative transfusion of >5 units of packed red cells, of early postoperative kidney failure, and of further deterioration of liver function tests after postoperative day 1. The conjunction of these events favored the development of, or reduced the tolerance to, additional complications, such as sepsis or upper gastrointestinal bleeding, that were responsible for the delayed occurrence of death.



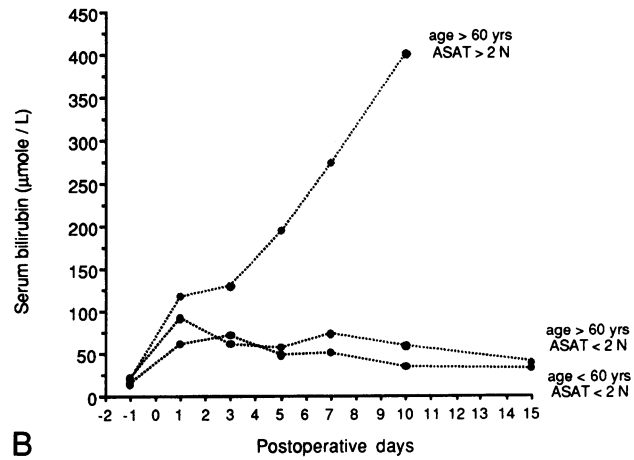




**Figure 2.** Postoperative kinetics of median prothrombin time (A) and serum bilirubin (B) in the 20 patients with cirrhosis undergoing a right hepatectomy for hepatocellular cancer, stratified by age and preoperative cytolysis. Age younger than 60 years and ASAT less than twice the normal upper range (2N) = 10 patients, age younger than 60 years and ASAT > 2N = 5 patients, age older than 60 years and ASAT > 2N = 5 patients. Patients who died after surgery were not excluded from analysis.

The preoperative increase in ASAT was most probably related to the necroinflammatory activity present in the nontumorous liver, because it was observed mainly in patients with HBV or HCV infection. The fact that the biologic witness of this activity, rather than its pathologic grading, influenced outcome is not surprising because the two parameters do not correlate in patients with a viral infection.[17] Periportal necrosis and portal inflammation are the markers that best predict the long-term outcome in patients with a viral infection. Our results suggest that these are less powerful than an increase in transaminase levels to assess the early risk associated with liver resection.

Patients with cirrhosis who are older than 60 years were also at increased risk of postoperative death, but these were also the only patients in whom preoperative ASAT was >2N. Because of this correlation, which is classic in patients with HCV infection, we cannot conclude that age is an independent risk factor. Age had in fact no influence on the incidence of postoperative complications, nor on the duration of postoperative liver failure in patients with cirrhosis with preoperative ASAT levels <2N. These results are concordant with the recent report that liver resection for hepatocellular cancer in the elderly can be performed with a low risk of postoperative complications.[18] We cannot, however, exclude the possibility that the slower regenerative response and limited reserve function associated with aging[19] impairs outcome.

In contrast to its influence in patients with cirrhosis, a preoperative increase in ASAT (or the necroinflammatory activity within the nontumorous liver) did not appear to have a significant impact in patients with a lower grade of fibrosis. In other words, chronic active hepatitis and cirrhosis contribute to increase the risk of a right hepatectomy, but neither parameter on its own has a significant impact.

In summary, a right hepatectomy results in a decrease in prothrombin time and an increase in serum bilirubin on postoperative day 1; the magnitude of these changes is not influenced by the characteristics of the nontumorous liver, in particular the severity of fibrosis. This liver failure resolves rapidly in patients with no or mild fibrosis but is associated with ascites and persists for 1 week in patients with bridging fibrosis (grade 3) and for several weeks in patients with cirrhosis (grade 4). Although this delay in recovery prolongs the hospital course, it does not, in itself, increase the risk of the surgical procedure. If, however, patients with grade 4 fibrosis (cirrhosis) also have a preoperative increase in ASAT > 2N, liver failure further deteriorates in the postoperative period, and a secondary fatal complication, such as sepsis or kidney failure, almost inevitably develops despite aggressive medical management.

We believe that the stratification based on the accurate grading of the severity of fibrosis and on the presence of a superimposed active hepatitis, assessed by preoperative serum ASAT, should be taken into account when assessing the risk associated with liver resection in patients with chronic liver disease and comparing the experience of different groups. Patients with increased transaminase levels should undergo a preoperative liver biopsy to assess the severity of fibrosis. If grade 4 fibrosis is present, these patients should not undergo a major liver resection such as a right hepatectomy; instead, they should undergo transplantation or be entered into trials investigating the potential benefit of preoperative antiviral therapy or portal vein embolization.[20]

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