The Risk of Surgery in Patients With Liver Disease

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Because of the multiple functions of the liver—synthesis of most serum proteins, metabolism of nutrients and drugs, excretion and detoxification of endogenous toxins and exogenous agents, and filtering of portal venous blood—assessing the risk of surgery in patients with liver disease is a challenging endeavor. Any or all of the functions of the liver may be impaired in patients with liver disease. As a result, the pharmacokinetic parameters of anesthetics, muscle relaxants, analgesics, and sedatives can be affected by changes in binding to plasma proteins, detoxification, and excretion; bleeding risk can be increased because of coagulopathy; and susceptibility to infection can be increased because of altered functioning of hepatic reticuloendothelial cells and other changes in the immune system as well as portal hypertension. Perhaps most importantly, a diseased liver is particularly susceptible to the hemodynamic changes that accompany surgery. On the other hand, operative risk is probably not increased in the vast majority of patients with liver disease, including most of those with chronic hepatitis C, in whom liver function is preserved.

Mild elevations of serum aminotransferase, alkaline phosphatase, or bilirubin levels are frequent after surgical procedures, whether performed under general, spinal, or epidural anesthesia. In patients without preexisting liver disease, these perturbations are usually transient, of no clinical significance, and often unnoticed. Clinically important hepatic dysfunction is more likely to occur in patients with preexisting liver disease. This review will consider the factors that contribute to perioperative hepatic dysfunction and prediction of operative risk in patients with liver disease undergoing surgery other than liver transplantation.

EFFECTS OF ANESTHESIA AND SURGERY ON THE LIVER

Anesthesia causes a moderate reduction in hepatic arterial blood flow and hepatic oxygen uptake; however, a clinical effect of these changes on healthy volunteers has not been shown. In one study, the reduction in hepatic blood flow during the first 30 minutes of anesthesia averaged 35% among 42 patients without liver disease. Interestingly, liver blood flow returned to baseline during surgery, a finding that raises the possibility that either the initial hypoperfusion or reperfusion injury, or both, may contribute to postoperative liver dysfunction when it occurs. Moreover, patients with liver disease are more likely than patients without liver disease to experience hepatic decompensation with anesthesia.

The volatile anesthetics halothane and enflurane reduce hepatic arterial blood flow as a result of systemic vasodilatation and a slightly negative inotropic effect. By contrast, these effects are minimal with isoflurane, which may actually increase hepatic arterial blood flow and is the preferred anesthetic agent in patients with liver disease. Moreover, isoflurane, as well as the newer haloalkanes desflurane and sevoflurane, undergo less hepatic metabolism (0.2% in the case of isoflurane) than either halothane (20%) or enflurane (2% to 4%), presumably accounting for a correspondingly lower risk of immunological drug-induced hepatitis.

Still, even the risk of halothane hepatitis is quite low at one in 35,000 exposures. Recently, the mechanism of halothane hepatitis was proposed to involve immune sensitization to trifluoropropylated proteins formed by oxidative metabolism of halothane by cytochrome P450 2E1 in genetically predisposed individuals. Such metabolism can be inhibited by prior administration of disulfiram. Risk factors for halothane hepatitis include obesity, female gender, multiple exposures to halothane, and a family history of similar occurrences. Hypercarbia initiates sympathetic stimulation of the splanchnic vasculature, thereby decreasing portal blood flow, and should be avoided in patients with liver disease. The PCO₂ should be maintained in the range of 35 to 40 mm Hg during surgery.

The actions of commonly used neuromuscular blocking agents may be prolonged in patients with liver disease because of reduced plasma pseudocholinesterase activity, decreased biliary excretion, and an increase in the volume of distribution. Atracurium has been recommended as the agent of choice in patients with liver disease or biliary obstruction, because its metabolism does not depend on the liver or kidneys. The long-acting nondepolarizing muscle relaxant, doxacurium, is recommended for prolonged surgical procedures including liver transplantation.

Because of reduced hepatic blood flow, the metabolism of morphine and meperidine may be decreased in patients with liver disease and portal hypertension, in contrast to fentanyl or sufentanil, which are the preferred narcotic agents. Similarly, the metabolism of the benzodiazepine sedatives, diazepam and chlordiazepoxide, can be prolonged in patients with liver disease, and oxazepam and lorazepam, which are eliminated by glucuronidation without hepatic metabolism, are preferred. Like benzodiazepines, barbiturates, which do not affect hepatic blood flow significantly, bind to γ-aminobutyric acid receptors in the brain, can precipitate hepatic encephalopathy, and must be used with caution in patients with liver disease. Although the metabolism of thiopental is decreased in patients with cirrhosis, plasma protein binding of thiopental is also decreased, so that total body clearance of the drug is unaltered in cirrhosis. Rare instances of usually cholestatic hepatotoxicity caused by benzodiazepines or barbiturates, including a syndrome of fever, hepatitis, lymphadenopathy, eosinophilia, and dermatitis, are no more likely in patients with liver disease than in those without liver disease. Chlorpromazine has a more depressant effect on the central nervous system in patients with liver dysfunction than in healthy subjects.

The nature of the surgical procedure itself may be the most
important determinant of postoperative hepatic dysfunction in patients with liver disease. For example, laparotomy leads to a greater reduction in hepatic arterial blood flow than does extra-abdominal surgery, in part because traction on the abdominal viscera may cause reflex systemic hypotension as a result of dilatation of capacitance vessels. The greater the degree of hemorrage with surgery, the greater the fall in hepatic blood flow and chance of ischemic injury to the liver. In patients with cirrhosis and previous abdominal surgery, adhesions around the liver can be highly vascular, leading to an increased risk of intraoperative bleeding. Morbidity and mortality rates are higher for emergent than elective surgery, and cholecystectomy, gastric surgery, and colectomy are associated with particularly high mortality rates in patients with decompensated cirrhosis. In the absence of ascites, subtotal cholecystectomy or cholecystostomy may be preferable to cholecystectomy in a patient with advanced cirrhosis and cholecystitis. On the other hand, laparoscopic cholecystectomy can be performed safely in selected patients with well-compensated cirrhosis and no signs of portal hypertension.

Limited experience suggests that cardiac surgery is associated with a high operative mortality rate in patients with cirrhosis. In a retrospective review of 13 patients with predominantly alcoholic cirrhosis undergoing often emergent coronary artery bypass grafting, valve replacement, or both, Klemperer et al. reported a postoperative mortality rate of 80% in those with Child's class B cirrhosis, but no mortality among those with Child's class A cirrhosis. The high mortality rate was attributed to a high risk of major postoperative infections and bleeding, rather than cardiac dysfunction. Risk factors for hepatic decompensation after cardiac surgery include the total time of cardiopulmonary bypass, use of nonpulsatile as opposed to pulsatile cardiopulmonary bypass, and need for perioperative pressor support. Cardiopulmonary bypass may particularly aggravate the coagulopathy of liver disease by inducing platelet dysfunction, fibrinolysis, and hypocalcemia. Patients with advanced cardiac fibrosis undergoing tricuspid valve replacement are thought to be at particular risk of postoperative liver failure if ligation of the inferior vena cava leads to an increase in caval pressure. In patients with advanced cirrhosis and cardiac disease, less invasive procedures such as angioplasty, valvuloplasty, or novel myocardial revascularization techniques are recommended. In rare instances, cardiac surgery followed by liver transplantation has been performed. Even more rarely, liver transplantation has been undertaken before cardiac surgery in patients with left ventricular dysfunction, but the risk of hemodynamic instability resulting from reduced venous return and reperfusion of the graft during liver transplantation makes this approach especially hazardous.

**ESTIMATING OPERATIVE RISK IN PATIENTS WITH LIVER DISEASE**

Precise estimates of operative risk in patients with well-characterized liver disease are hard to come by. Most available data derive from relatively small retrospective studies of cirrhotic patients undergoing abdominal surgery. Few studies have examined surgical risk in patients with acute viral, chronic, or alcoholic hepatitis, and some of the available data actually predate the availability of modern serological testing and hepatobiliary imaging. Contraindications to elective surgery in patients with liver disease are listed in Table 1.

**TABLE 1. Contraindications to Elective Surgery in Patients With Liver Disease**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Acute viral hepatitis</td>
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<td>Acute alcoholic hepatitis</td>
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<tr>
<td>Fulminant hepatic failure</td>
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<tr>
<td>Severe chronic hepatitis</td>
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<tr>
<td>Child's class C cirrhosis</td>
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<tr>
<td>Severe coagulopathy (prolongation of the prothrombin time of &gt;3 seconds despite vitamin K administration; platelet count &lt; 50,000/mm³)</td>
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<td>Severe extrahepatic complications</td>
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<tr>
<td>Hypoxemia</td>
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<tr>
<td>Cardiomyopathy, heart failure</td>
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<tr>
<td>Acute renal failure</td>
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**Hepatitis.** Acute hepatitis is considered to be a contraindication to elective surgery. This recommendation is based on older studies in which operative mortality rates of 9.5% to 13% were reported in icteric patients who underwent laparotomy as part of a diagnostic evaluation that led to a diagnosis of acute viral hepatitis; such patients do not undergo diagnostic laparotomy nowadays. Elective surgery is also contraindicated in patients with histological evidence of alcoholic hepatitis, in whom mortality rates as high as 55% have been reported in patients undergoing open liver biopsy or portosystemic shunt surgery.

**Chronic Hepatitis.** In patients with chronic hepatitis, surgical risk appears to correlate with the clinical, biochemical, and histological severity of disease. Elective surgery has been reported to be safe in patients with asymptomatic mild chronic hepatitis (formerly chronic persistent hepatitis), whereas patients with symptomatic and histologically severe chronic hepatitis have an increased surgical risk, particularly if hepatic synthetic or excretory function is impaired, portal hypertension is present, or bridging or multilobular necrosis is seen on liver biopsy specimens. Moreover, patients with severe histological activity have been reported to have a higher rate of tumor recurrence after resection of hepatocellular carcinoma compared with patients with mild inflammation.

**Fatty Liver and Nonalcoholic Steatohepatitis.** In contrast to alcoholic hepatitis, alcoholic or nonalcoholic fatty liver does not appear to contraindicate elective surgery, although a trend toward increased mortality following hepatic resection has been reported for patients with moderate to severe steatosis (>30% of hepatocytes containing fat). In any event, a period of abstinence from alcohol before surgery is advisable because of the potential perioperative complications of alcoholism, including alcohol withdrawal in the postoperative period, enhancement of halothane hepatotoxicity by alcohol as shown in an animal model, and the possibility of toxicity with therapeutic doses of acetaminophen (often used for analgesia in the postoperative period) in alcoholics.

Cirrhosis, due presumably to nonalcoholic steatohepatitis, may be found unexpectedly in up to 6% of patients undergoing gastric bypass surgery for morbid obesity. Most surgeons do not view the discovery of subclinical cirrhosis at surgery to be a contraindication to proceeding with gastric bypass surgery despite a reported perioperative mortality rate of 4% in this group of patients.

**Other Causes of Liver Disease.** In patients with autoimmune hepatitis in remission, elective surgery is well tolerated in patients with compensated liver disease, but perioperative
administration of “stress” doses of hydrocortisone is indicated in patients taking prednisone. Patients with cirrhosis caused by hemochromatosis may require monitoring of diabetes in the perioperative period and should be evaluated carefully for the possibility of cardiomyopathy, which increases surgical risk, as suggested by recent experience with liver transplantation in patients with hemochromatosis. In patients with Wilson’s disease, neuropsychiatric involvement may interfere with the ability of the patient to provide informed consent, and surgery may precipitate or aggravate neurological symptoms. Moreover, D-penicillamine interferes with the cross-linking of collagen and may impair wound healing, so the dose should be decreased in the first 1 to 2 postoperative weeks.

**Cirrhosis.** Most available data on the risk of surgery in patients with liver disease pertain to cirrhosis<sup>26,27,49,53-67</sup> (Table 2). A number of retrospective studies have shown that perioperative mortality and morbidity rates correlate well with the Child-Turcotte<sup>68</sup> or Child-Pugh<sup>67,69</sup> class of cirrhosis. In a review of 100 patients with predominantly alcoholic-induced cirrhosis undergoing abdominal surgery, Garrison et al. in 1984 reported perioperative mortality rates of 10%, 31%, and 76% for patients classified as Child’s class A, B, and C, respectively. Among 52 parameters assessed in a multivariate analysis, the Child classification was the best predictor of surgical mortality and morbidity. In a similar study by Mansour et al. in 1997, nearly identical results were described in 92 patients with cirrhosis (approximately 50% alcoholic and 50% nonalcoholic) undergoing abdominal surgery, with mortality rates of 10%, 30%, and 82% in patients classified as Child’s class A, B, and C, respectively. These and other studies have also observed increased surgical risk in patients undergoing emergent as opposed to elective surgery; abdominal operations, particularly biliary tract surgery; and hepatic resection (see below). Some studies have not confirmed the predictive value of the Child classification, in part because few Child’s class C patients were included, nor has any study validated the predictive value of the Child’s class prospectively.<sup>64,66</sup>

**Table 2. Risk Factors for Morbidity and Mortality in Patients With Cirrhosis Undergoing Surgery**

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Characteristic of patient</th>
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<tr>
<td>Emergent</td>
<td>Child’s class (C &gt; B)</td>
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<tr>
<td>Abdominal, especially cholecystectomy</td>
<td>Ascites</td>
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<tr>
<td>gastric resection, or colectomy</td>
<td>Infection</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Anemia</td>
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<tr>
<td>Hepatic resection</td>
<td>Malnutrition</td>
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<tr>
<td></td>
<td>Jaundice</td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>Hypoalbuminemia</td>
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<tr>
<td></td>
<td>Portal hypertension</td>
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<tr>
<td></td>
<td>Prolonged prothrombin time (&gt;2.5 sec above control) that does not correct with vitamin K</td>
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<tr>
<td></td>
<td>Abnormal quantitative liver function tests (e.g., galactose elimination capacity, aminopyrine breath test, indocyanine green clearance, monoethylglycinexylylidel test)</td>
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<tr>
<td></td>
<td>Hypoxemia</td>
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Although there are no prospective studies showing improved surgical outcome after preoperative interventions to improve hepatic function, widely accepted guidelines are that elective surgery is well tolerated in patients with Child’s class A cirrhosis, permissible with preoperative preparation in patients with Child’s class B cirrhosis (except those undergoing extensive hepatic resection or cardiac surgery), and contraindicated in patients with Child’s class C cirrhosis.<sup>70</sup> Quantitative assessment of liver function with dynamic tests such as galactose elimination capacity, aminopyrine breath testing, indocyanine green clearance, and the rate of metabolism of lidocaine to monoethylglycinexylylidel has also been reported to predict perioperative morbidity and mortality in patients with cirrhosis, but these tests have not been shown convincingly to provide additional prognostic information over that provided by the Child-Pugh classification, nor have they gained widespread clinical acceptance.<sup>71</sup> Although the Acute Physiology, Age, and Chronic Health Evaluation System (APACHE III) has been shown to predict survival in cirrhotic patients admitted to an intensive care unit, the system has not been studied specifically in cirrhotic patients undergoing surgery.<sup>72</sup>

Respiratory compromise in patients with liver disease may result from the hepatopulmonary syndrome (chronic liver disease, increased alveolar-arterial gradient while breathing room air, and evidence of intrapulmonary vascular dilatation), restrictive lung disease caused by ascites or pleural effusions, pulmonary hypertension, and immune-mediated lung disease associated with autoimmune liver diseases.<sup>73</sup> Severe hypoxemia (pO<sub>2</sub> < 60 mm Hg) associated with liver disease is generally considered a relative contraindication to surgery (except for liver transplantation in patients with hepatopulmonary syndrome). Fortunately, severe hypoxemia is rare in patients with liver disease.<sup>74</sup> In a recent multivariate analysis, a diagnosis of chronic obstructive lung disease and surgery on the respiratory tract were identified as risk factors for mortality in patients with cirrhosis undergoing surgery.<sup>57</sup> A higher-than-usual concentration of oxygen during anesthesia is recommended in patients with cirrhosis.<sup>8</sup>

### RESECTION FOR HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is a well-established complication of long-standing cirrhosis, with an estimated annual incidence of 3% to 5%.<sup>75-77</sup> In the past, cirrhosis was considered to be a contraindication to resection of hepatic tumors, with reported perioperative mortality rates as high as 50%. With better patient selection (including earlier detection of tumors), meticulous preoperative preparation, intensive intraoperative and postoperative monitoring, and improved surgical techniques, the perioperative mortality rate for hepatic resection has decreased to 3% to 16%, although postoperative morbidity rates are still as high as 60%, 5-year recurrence rates are as high as 100%, and 5-year survival rates are no higher than 50%.<sup>75-82</sup> The Child’s classification is still the most widely used measure of operability, but studies have failed to confirm its value in predicting morbidity and mortality, in part because of selection bias and the small number of patients with Child’s class B and C cirrhosis studied.<sup>78</sup>

Although Child’s class A patients tolerate hepatic resection well, a recent study has suggested that up to 60% of patients with Child’s class A cirrhosis associated with portal hypertension, as measured by a hepatic venous pressure gradient of
>10 mm Hg, experience hepatic decompensation (ascites, jaundice, or encephalopathy) after hepatic resection for hepatocellular carcinoma. Additional risk factors for morbidity after hepatic resection include thoracotomy, pulmonary disease, diabetes mellitus, malignancy, and complex intrahepatic inflammatory disease. Alternative methods of quantitating hepatic reserve, including quantitative liver function tests, indocyanine green clearance, uptake of radiolabeled gold colloid by Kupffer cells, liver scintigraphy using technetium-99m-galactosyl human serum albumin, and measurement of hepatic volume by computed tomography, have not gained wide acceptance. The question of whether patients with Child's class A cirrhosis and a small hepatocellular carcinoma should undergo liver transplantation instead of surgical resection remains controversial. Cryosurgery has been used in patients with hepatic neoplasms not amenable to surgical resection, such as those with multiple lesions abutting on major blood vessels. Experience with this technique is limited, but the complications are the same as those for hepatic resection, including hemorrhage, abscess, pleural effusion, bile leak, and hepatic failure.

**Surgery in Patients with Obstructive Jaundice**

The perioperative mortality rate in patients with obstructive jaundice has been reported to range from 8% to 28%. In a large retrospective study of 373 patients undergoing surgery for obstructive jaundice before 1983, the perioperative mortality rate was 9.1%, and multivariate analysis identified three predictors of postoperative mortality: an initial hematocrit value less than 30%, an initial serum bilirubin level greater than 200 μmol/L (11 mg/dL), and a malignant cause of obstruction (e.g., pancreatic carcinoma or cholangiocarcinoma). When all three factors were present, the mortality rate approached 60%, whereas when none was present, the mortality rate was only 5%. Other preoperative predictors of poor surgical outcome in these patients include azotemia, hypoalbuminemia, and cholangitis (Table 3). Perioperative complications in patients with obstructive jaundice include infections, resulting in part from bacterial colonization of the biliary tree, impaired Kupffer cell function, defective neutrophil function, and a high rate of endotoxia, renal failure, stress ulceration, disseminated intravascular coagulation, endotoxia, renal failure is particularly common, with a mean reported frequency of 8% to 28%. There is limited evidence that perioperative oral administration of ursodeoxycholic acid or lactulose may prevent endotoxia and reduce the likelihood of postoperative complications.

**Preoperative Evaluation and Postoperative Monitoring**

Whether otherwise healthy surgical candidates should be screened for unsuspected abnormalities of liver function tests is controversial; abnormalities will be detected in approximately 1 in 700 such individuals. On the other hand, evaluation of any patient undergoing surgery should include careful history-taking to identify risk factors for liver disease, including previous blood transfusions, tattoos, illicit drug use, sexual promiscuity, a family history of jaundice or liver disease, a history of jaundice or fever after anesthesia, alcohol use, and a complete review of current medications. Symptoms or findings on physical examination suggestive of liver disease, including fatigue, pruritus, increased abdominal girth, jaundice, palmar erythema, spider telangiectases, splenomegaly, and gynecomastia and testicular atrophy in men, should be evaluated.

In patients known to have liver disease, it is important to identify the presence of jaundice, ascites, or encephalopathy, to obtain a complete biochemical assessment of liver function, and, if necessary, evaluate the patient for the cause of liver disease. Coagulopathy, ascites, and encephalopathy may require specific treatment before surgery. Repletion of vitamin K, infusions of fresh frozen plasma to correct the prothrombin time to within 3 seconds of normal, and transfusions of platelets to maintain a count of at least 100,000/mm² are recommended.

| Table 3. Risk Factors for Operative Mortality in Patients With Obstructive Jaundice |
|-----------------|-----------------|
| **Hematocrit value <30%** |
| **Serum bilirubin level >11 mg/dL** |
| **Malignant cause of biliary obstruction** |
| **Azotemia** |
| **Hypoalbuminemia** |
| **Cholangitis** |

A prolonged bleeding time can also be treated with diamino-8-o-arginine vasopressin. In general, because of the possibility of postoperative wound dehiscence and abdominal wall herniation, ascites should be treated aggressively before abdominal surgery; if necessary, the ascites can be drained completely at laparotomy. Although there is no evidence that prophylactic therapy to prevent encephalopathy is beneficial in patients with liver disease, it is important to recognize overt encephalopathy preoperatively, because of the high frequency of conditions that precipitate or exacerbate encephalopathy in the postoperative period, including constipation, alkalosis, use of central nervous system depressants, and withdrawal from narcotic analgesics.
system depressants, hypoxia, sepsis, azotemia, and gastrointestinal bleeding. Preoperative identification, evaluation, and management of renal dysfunction are equally critical. Although gastroesophageal varices that have bled should be treated in the usual manner, there are no clear data to suggest that surgery leads to an increased risk of variceal bleeding in the postoperative period, although fluid overload should be avoided. In the cirrhotic patient with malnutrition, there is limited evidence that peroperative nutritional support may reduce the frequency of postoperative complications and short-term mortality but does not improve long-term survival after hepatic resection.122-124 Percutaneous gastrostomy is contraindicated in patients with ascites and should generally be avoided in patients with portal hypertension.

In the postoperative period, the patient with liver disease should be observed closely for signs of hepatic decompensation, including worsening of jaundice, encephalopathy, and ascites. The prothrombin time and serum bilirubin level are probably the best measures of hepatic function, although the serum bilirubin can be expected to rise initially, particularly after complicated surgery, multiple blood transfusions, excessive bleeding, hemodynamic instability, or systemic infection. Renal function should be monitored as well because of the risk of hepatorenal syndrome. Serum glucose levels should be followed closely, because hypoglycemia often accompanies postoperative liver failure.

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REFERENCES


