9 Morbidity and Mortality After Liver Surgery

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- *The historical high morbidity and mortality rates associated with liver resections has decreased significantly over time. The pattern of complications has also changed. Massive intraoperative blood loss has become very rare, but other complications such as bile leak remain high.*
- *Modern methods to prevent blood loss, especially allogeneic blood transfusion, include the use of intraoperative low central venous pressure, various methods of vascular clamping, intraoperative blood salvage, preoperative autologous donation, acute intraoperative normovolemic hemodilution, and efficient modalities of parenchymal transection.*
- *Postoperative liver failure is one of the most serious complications after a hepatectomy. Although uncommon, it is associated with high mortality. Knowledge of risk factors is crucial because prevention is the best approach to avoid mortality. However, early identification of liver failure allows for some effective measures.*
- *Bile leak is the most common biliary complication after liver resections. Most resolve with conservative approaches, and the need for surgical approach is associated with higher mortality rates. Proper intraoperative detection and closure of bile leaks is essential to prevent postoperative biliary fistula.*

INTRODUCTION

MORTALITY AFTER HEPATECTOMY

There has been a marked improvement in the safety of liver resections in recent decades. Mortality rates after liver resections have reduced from 13-30% in the 1970s to less than 5%, and even no mortality, at present.[1–3] A recently published series of 4,152 liver resections at Memorial Sloan Kettering reported a 90-day mortality rate that decreased from 5% before 1999 (1993 to 1999), to 2.3% between 2000 and 2006, and to 1.6% after 2007 (2007 to 2012).[3]

However, some important points should be considered when evaluating the risk of a hepatectomy. First, until recently, most studies on liver resections have considered operative mortality to be death occurring during hospital stay (in-hospital mortality) or up to 30 days after surgery. This definition is useful in conditions of high mortality, such as the case of hepatectomies until the 1980s. Nonetheless, deaths related to surgery may occur later depending on several factors, such as those related to hepatic regeneration. Thus, the 90-day mortality rate has been suggested to evaluate risk with liver surgery.[4,5] Mayo et al.,[5] using a linked SEER (Surveillance, Epidemiology and End Results)-Medicare database, demonstrated that the rate of 90-day mortality was almost twice that of 30-day mortality (10.1% vs. 5.7% for the whole group). After resection of HCC and CRLM, 30-day and 90-day mortality rates were 9.7% vs. 15% and 4.3% vs. 8.4%, respectively.

Second, most reports on mortality following liver

resections have come from single high-volume institutions that are experts in hepatobiliary surgery. Modern large single-institution series report mortality rates of 0-1.3%.[2] Population-based analyses using administrative data usually identify higher mortality rates.[6] In a literature review, van den Broek et al.[7] reported a mean operative mortality rate of 1% after liver resections; however, a large computer-based study in the United States including 2,313 open hepatectomies found a 30-day mortality rate of 2.5%.[8] In another large study using a computer database of all liver resections in France, Farges et al.[4] reported a 90-day mortality rate of 5.8%.

Third, the characteristics of patients undergoing liver resection is variable across published series. There has been an increase in the proportion of liver resections for malignancies, mainly colorectal liver metastases, hepatocellular carcinoma, and biliary tumors. Such patients are more likely to demonstrate pathological changes in the underlying parenchyma, such as fibrosis, steatosis, and chemotherapy-associated liver injury.[9–12] Dokmak et al.[12] reported a six-fold higher risk for mortality in patients operated on for malignant disease (0.7% vs. 4.5% for benign vs. malignant diseases, respectively).

Thus, mortality after liver resections is related, among several other factors, to the definition of surgical mortality and patient features. Despite a clear reduction in risk, mortality remains significant after hepatectomy, at least in part as a result of an increasing proportion of major resections in patients with malignancy.[12]

MORBIDITY AFTER HEPATECTOMY

Despite a clear reduction in mortality after hepatectomy, morbidity remains frequent and complications still occur in 20-45% of patients in large series of hepatectomies.[3,7,13–22] This high morbidity despite the advances in liver surgery could be at least partially explained by the increasing complexity of procedures. Indeed, complications leading to death have shifted from bleeding, in the early days of hepatectomies, to liver failure, in the present. The risk of complications after a hepatectomy is mainly dependent on factors concerning the patient (such as comorbidities), the surgery (such as extent of resection and blood loss), and the liver parenchyma status (such as the presence of cirrhosis).

Nil morbidity was reported in some series of laparoscopic liver resections in strictly selected patients. However, even in healthy patients with normal livers (in the case of living liver donors), hepatectomy has been associated with relatively high rates of morbidity.

Standard definition and adequate stratification of severity of postoperative complications are essential to compare efficacy of different techniques and measures, especially among diverse institutions worldwide.

The general system for assessment of severity of morbidity proposed by Clavien et al.[23] (Clavien-Dindo classification) focuses on therapeutic consequences of morbidity, and it is appropriate for liver resections. Complications are scaled according their severity, from grade I to V. Grade I and II refer to minor complications, grade III and IV major complications, and grade V fatal complications (**Table 1)**. While Clavien-Dindo classification is probably the best system available for stratification of severity of complications, it does not take into account particularities of complications. Thus, it is very useful as a means of evaluating and comparing global results, but it lacks specificity to evaluate the efficacy of some measures, for example. The International Study Group of Liver Surgery (ISGLS) has attempted to standardize definition and grading of the most common specific postoperative complications for liver resections, as discussed below in specific topics in this chapter. The main surgery-specific complications after liver resections include postoperative liver failure, bile leak hemorrhage, and surgical site infection.

Complications after liver resection can lead to fatal early outcomes, especially when postoperative liver failure and/or sepsis occur. However, beyond this obviously early consequence, perioperative complications may result in longer hospital stays, increasing costs, and higher recurrence rates in oncological patients.

Table 1. ISGLS definition and grading of post-hepatectomy hemorrhage.

DEFINITION
1- Drop in hemoglobin > 3g/dL after establishing a postoperative baseline
2- Any postoperative transfusion for a failing hemoglobin and/or the need for any reintervention (embolization or re-laparotomy) to stop bleeding
3- Evidence of bleeding, such as blood loss via drains or active hemorrhage by imaging.
GRADING
Grade A- Bleeding requiring transfusion of up 2 units PRCBs
Grade B- Bleeding requiring transfusion of > 2 units PRBCs but without invasive intervention
Grade C- Bleeding requiring immediate postoperative transfusion secondary to intraoperative blood loss

ISGLS: International Study Group of Liver Surgery, PRBCs: packed red blood cells. (From Rahbari et al.[146])

RISK FACTORS ON LIVER RESECTIONS

Well-established risk factors in liver resections include those related to the patient (such as presence of comorbidities, malignancy, and obesity), to surgery (such as extent of resection, intraoperative bleeding, and simultaneous extrahepatic procedures), and to liver parenchyma status (such as cirrhosis, steatosis, chemotherapy-associated liver injury, and cholestasis).[24–26]

The presence of **underlying chronic liver disease**, especially cirrhosis, has been clearly identified as a risk factor in liver resection.

Cirrhosis is the most obvious underlying liver disease that increases the risk of a hepatectomy. The limited capacity of liver regeneration, the smaller functional reserve of the remnant liver, and the increased risk of perioperative blood loss are all responsible for an increased risk of postoperative liver failure in cirrhotic patients. Estimating surgical risk in patients with cirrhosis is challenging, and depends on the degree of hepatic dysfunction, the extent of liver resection, and the presence of comorbidities. Most liver resections in patients with cirrhosis are performed to treat hepatocellular carcinoma, and morbidity rates are 26-56%.[27–29] Mortality rates after major and minor hepatectomies in selected patients with cirrhosis are up to 25% and 3%, respectively.[18,30,31] In fact, postoperative outcomes in cirrhotic patients are markedly influenced by the severity of the underlying liver disease and the extent of liver resection being considered.[32–34]

Thus, cirrhosis requires an individualized preoperative assessment, as discussed in detail in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection) and **Chapter 6** (Surgical Approach to the Patient with Cirrhosis). In summary, several methods for liver function assessment before liver resection have been used. Risk stratification based on Child-Pugh (**Table 1)** and MELD (model for end-stage liver disease) (**Table 2**) scores have been used to estimate risk and select cirrhotic patients for surgery, leading to lower mortality rates. Despite conflicting reports, a MELD score greater than 8 has been accepted as a high risk factor.[35] Child-Pugh score A patients usually tolerate a major hepatectomy; however, patients with B and C scores have an increased risk and should undergo only minor hepatectomies or tumor enucleation, respectively.[35,36] The presence of portal hypertension has been discussed as a risk factor for hepatectomy in cirrhotic patients, but it has not been found as an independent predictive risk factor.

Table 2. Score of severity for postoperative liver failure.

Points	0	1	2
Total serum bilirubin (μmol/L)	≤ 20	21-60	> 60
Prothrombin time (seconds above normal)	< 4	4-6	> 6
Serum lactate (mmol/L)	≤ 1.5	1.6-3.5	>3.5
Encephalopathy severity grade	None	1 and 2	3 and 4

PLF: none (0 points), mild (1-2 points), moderate (3-4 points), severe (>4 points). (Adapted from Schindl et al.[127])

Chemotherapy-associated liver injuries, such as sinusoidal dilatation and steatohepatitis, occur mainly in oxaliplatin-based and irinotecan-based chemotherapy, respectively.[37] These hepatic injuries and steatosis have been associated with worse surgical mortality rates and postoperative liver failure after hepatectomy, mainly for colorectal liver metastases (see **Chapter 4** – Underlying Liver Disorders in Hepatic Surgery).[11,38–40]

Extensive liver resections, and more precisely small remnant liver, are associated with higher operative risk. The minimum safe volume of remnant liver is 25% of the total functional liver volume in patients with an otherwise normal liver. However, when underlying chronic liver disease is present, this cutoff should be higher, such as 40% in the case of chemotherapy-associated injury or cirrhosis.[41] The precise determination of the minimum safe future remnant liver is challenging when underlying chronic liver disease is present, because hepatocyte function varies according to the degree of parenchymal injury. Thus, a variety of liver function tests have been investigated to estimate parenchymal liver function. One of the most widely described is the indocyanine green retention at 15 min test (ICGR-15). Patients with a retention of less than 10% of indocyanine green at 15 minutes after infusion (ICGR-15<10%) could undergo extensive hepatic resection, while patients with ICGR-15≥30% should undergo only limited non-anatomical resections.[42] Other function tests include the LiMAx test (which measures cytochrome P450 activity by the ratio of exhaled $^{13}CO_2$:$^{12}CO_2$) and hepatobiliary scintigraphy (using measures of uptake and excretion of ^{99m}Tc-mebrofenin).[43]

Dynamic magnetic resonance imaging (MRI) techniques are promising methods to evaluate parenchymal function in different regions of the liver. Methods taking into account intrahepatic regional differences of liver function could help the technical planning of hepatectomies.[44]

BLOOD LOSS AND BLOOD TRANSFUSION

INTRODUCTION

Bleeding was the most feared complication of a hepatectomy in the 1970s, when it was responsible for one third of operative deaths. Before 1990, transfusion requirement during liver resection was roughly 90%. Currently, although major hemorrhagic complications have become uncommon, transfusion requirement is present in 5-49% of hepatectomies. Given the probable association of blood transfusion with

adverse outcomes, blood loss and blood transfusion remain a crucial topic concerning operative morbidity.[1,14–16,22,45–47]

Both blood loss and allogeneic blood transfusion have deleterious effects. Allogeneic blood transfusion has a potential immunosuppressive effect,[48,49] with reduction of the activity of natural killer cells and of T lymphocyte blastogenesis, and increase of the activity of suppressor T lymphocyte. These changes could result in diminished resistance to infections[47,50] and easier proliferation of malignant cells.[51] In fact, studies have found a relevant association between transfusion and postoperative morbidity, specifically infectious complications, and also with tumor recurrence and long-term mortality.[52,53] Allogeneic blood transfusion has also been associated with acute lung injury, perioperative myocardial infarction, postoperative low-output cardiac failure, and increased operative mortality.[14,16,46,50,54–56]

Post-hepatectomy bleeding occurs at a rate of 0.6% to 8%. Definitions of postoperative hemorrhage and its severity are challenging to establish. A standard definition and grading system of postoperative hemorrhage was proposed by the International Study Group of Liver Surgery (ISGLS), as shown in **Table 1**.[57–59] This definition was validated in a large sample (835 patients) that found mortality rates of 0%, 17%, and 50% for grades A, B, and C hemorrhage, respectively.[57]

Risk factors for bleeding and blood transfusion include factors related both to the tumor (in cases of malignancy) and to the patient. A well-known risk for hemorrhage is cirrhosis, which is present in most patients undergoing hepatectomy for hepatocellular carcinoma. Among these patients, low prothrombin activity (<70%), centrally located tumors, involvement of hepatic veins, obesity (body mass index >23 kg/m^2), and major resection were identified as risk factors for severe blood loss (more than 1,500 mL).[60] Avoiding blood transfusion, notwithstanding blood loss, could be helpful. However, indications for blood transfusion are quite variable in the literature. Cunningham et al.[61] used a decrease in hematocrit to 24% in patients without antecedent cardiac disease and a decrease to 29% in patients with cardiac disease as criteria for blood transfusion in liver resection. Other indications were a total volume blood loss of more than 20% and/or hemodynamic instability, hemoglobin less than 8 g/dL, or symptomatic patients with hemoglobin of 8 to 9 g/dL.[47]

BLOOD TRANSFUSION AND MALIGNANCIES

Despite the association of blood loss and blood requirement with poorer oncological outcomes, this topic remains controversial.[62–65]

Concerning hepatic malignancies, most studies cover **hepatocellular carcinoma** resection, since this type of tumor occurs almost exclusively in patients with chronic underlying liver disease – mainly cirrhosis, a well-known risk factor for perioperative bleeding. In this setting, perioperative blood loss and blood transfusion have been associated with poor overall and disease-free survival rates.[66–71] The deleterious effect of blood transfusion on long-term survival has been demonstrated for both advanced HCC (tumors larger than 10 cm in diameter)[72] and early HCC.[73,74] Katz et al.[70] showed a significant inverse correlation between estimated blood loss and disease-specific survival. In fact, in this study, blood loss was the only significant factor associated with worse disease-free survival. In a French study[75] including 209 consecutive patients undergoing liver resection for HCC, blood loss was also an independent risk factor for tumor recurrence and short overall survival.

Concerning liver resections for **colorectal liver metastases**, few studies have focused on the oncological effects of blood transfusion, and the results are less consistent. In a study of more than 1,300 patients treated for colorectal liver metastases, Kooby et al.[50] observed an association between blood transfusion and postoperative complications, in a dose-related effect. However, it was not a significant predictor of long-term survival. On the other hand, Stephenson et al.[76] in a series of 55 patients found a higher rate of recurrence after resection of hepatic colorectal metastases in patients that needed blood transfusion. It is worth noting that postoperative infectious complications, which also suffer the influence of immunosuppressive effects of blood transfusion, were associated with poor long-term outcomes. Farid et al.[47] evaluated outcomes of 705 liver resections for colorectal liver metastases, and found a poorer overall and disease-free five-year survival when complications were present (24% vs. 37% and 13% vs. 26%, respectively). In this study, blood transfusion and postoperative sepsis were independent factors associated with long-term survival. There is no convincing support nowadays for the deleterious effect of blood transfusion on recurrence or long-term survival after resection of colorectal liver metastases, but postoperative morbidity (comprising hemorrhage) has been associated with poor oncological outcomes.[47,77,78]

There are few studies evaluating the effect of perioperative blood transfusion or blood loss in patients undergoing liver resection for **cholangiocarcinoma**. Nagino et al.[79] observed a higher incidence of complications when allogeneic blood transfusion was required in a series of 100 hepatic resections for hilar cholangiocarcinoma. Recently, Ercolani et al.[80] identified that patients operated on for intrahepatic cholangiocarcinoma had a better prognosis when no blood transfusion was necessary.

It is still debatable whether blood loss and blood transfusion are responsible themselves for poorer outcomes. Other factors could be responsible for impairment of the immune system in patients with large-scale blood loss, such as intraoperative hypotension, duration of anesthesia, stage of malignancy, and degree of liver dysfunction, among others.

Major surgery per se has an immunosuppressive effect, and blood transfusion could reflect a more extensive procedure, resulting in greater need for blood transfusion.[81]

MINIMIZING BLOOD LOSS AND ALLOGENEIC BLOOD REQUIREMENT

Prevention of bleeding and blood transfusion includes an adequate preoperative evaluation. A careful drug history is taken, and drugs such as aspirin, clopidrogrel, or warfarin should be stopped before surgery. Coagulation abnormalities should also be corrected before hepatectomy, especially in jaundiced or cirrhotic patients.

The use of antifibrinolytic agents, such as inhibitors of plasmin (aprotinin and nafamostat mesylate) and inhibitors of plasminogen (tranexamic acid and epsilon-aminocaproic acid), and procoagulant agents (recombinant factor VIIa), have been evaluated in liver resections with conflicting results.[82–84]

Similarly, the use of topical sealants over the cross-section area remains a controversial topic. They stimulate hemostasis by mimicking coagulation (i.e., fibrin sealants), providing a matrix for endogenous coagulation (i.e., collagen, felatin, cellulose sponges), or both.[85] There is no consensus as to whether these agents should be routinely used to prevent blood transfusion.

Other strategies with the goal of avoiding allogeneic blood transfusion and its consequences include techniques to minimize blood loss during surgery (such as the use of **low central venous pressure** and **vascular clamping**) and techniques of autologous donation (such as **intraoperative autotransfusion**, **acute normovolemic hemodilution**, and **preoperative autodonation**).

Low central venous pressure

Central venous pressure (CVP) is an indirect measure of pressure into the hepatic veins and a low CVP (<5 cmH_2O) is a useful method to avoid backflow bleeding from hepatic veins during liver transection. [86–91]

Several approaches enable reaching and maintaining a low CVP during surgery. Crystalloid and colloid restriction and the use of diuretics (furosemide) helps maintain patients in a hypovolemic state. If necessary (arterial hypotension), intravenous dopamine is associated with maintaining systolic blood pressure above 90 mmHg.[90,91] Reduced mechanical ventilation tidal volume and administration of a sufficient amount of muscle relaxant work together to reduce the CVP. Extradural blockade and systemic nitroglycerine infusion can also be used.[90] Intraoperatively, partial or total clamping of the infrahepatic vena cava can be used for this purpose.[92–94] Another measure is placing the patient in the Trendelenburg position (15° head-down).[87]

Despite the well-established reduction of blood loss, low CVP carries a potential higher risk for complications such as air embolism, systemic tissue hypoperfusion, and renal failure,[87,95] and should be used carefully in patients with underlying chronic liver disease, such as cirrhosis.

Vascular clamping

Vascular clamping is an effective way to minimize blood loss and avoid transfusion during liver transection. This topic is discussed in more detail in **Chapter 23** (Vascular Control and Parenchymal Transection Techniques). Since the first description of pedicular clamping by Pringle in 1908,[96] different modalities of vascular occlusion have been developed. The main strategies comprise inflow vascular occlusion and total vascular occlusion. Inflow occlusion can be total or selective (hemihepatic or segmental), continuous or intermittent, and associated or not with outflow occlusion (such as in the case of hepatic vascular exclusion). Clamping of the infrahepatic vena cava (partial or complete) can be used alone or in combination with inflow clamping to reduce bleeding during hepatic transection by reducing CVP.[97–101]

The benefit of vascular occlusion in reduction of blood loss seems clear. However, prolonged hepatic ischemia can be responsible for major complications, such as postoperative liver failure and ischemia-reperfusion syndrome. To avoid these complications, beyond the use of intermittent clamping (whenever possible), hypothermia or preconditioning can be combined with some techniques of vascular clamping to minimize parenchymal injury by the prolonged ischemia.[102]

Intraoperative blood salvage

Intraoperative blood salvage and autotransfusion consist of recovering blood lost during surgery and re-infusing it, generally just after the period that is more susceptible to bleeding.

Various medical devices have been developed to collect blood lost during surgery and re-infuse it by a venous access. The lost blood is collected, heparinized saline solution is added, and the blood is then passed through a filter and collected in a reservoir. Red blood cells are separated by centrifugation and then washed and filtered across a semi-permeable membrane, which removes components such as free hemoglobin, plasma, platelets, white blood cells, and heparin. The salvaged blood cells are re-infused up to six hours after.

The use of intraoperative blood salvage in oncological surgery is controversial because tumor cells are identified in the blood collected before reinfusion, representing a potential risk of disseminating metastasis. However, despite the identification of malignant cells in the collected blood, there is no clinical evidence of increased recurrence rate or poorer long-term survival with the use of blood salvage in oncological patients. The use of "cell processors", which wash and save red blood cells, and the use of hemofiltration (or ultrafiltration) seem to reduce the risk of reinfusion of

malignant cells. Nevertheless, no guidelines are available concerning the use of blood salvage devices during surgery for liver cancer.[103]

Preoperative autologous blood donation

Preoperative autologous transfusion consists of withdrawing blood from the patient for a period of days or weeks before the surgery and re-infusing the collected blood during surgery or after that, if necessary.

The main goal of this procedure is avoid the potential risks of allogeneic transfusion. Moreover, an additional benefit of autologous blood donation would be the stimulation of erythropoiesis mediated by an increase in the endogenous erythropoietin level, resulting in an accelerated rate of recovery of hemoglobin after surgery. A similar effect is observed in acute normovolemic hemodilution, as described below.

Patients can donate up to one unit (approximately 450 mL) twice weekly, until 72 hours before surgery. Autologous blood transfusion can be accompanied by the use of recombinant human erythropoietin to minimize preoperative decreases in hematocrit due to blood donation.

Shinozuka et al.[104] reported a reduction in the necessity of homologous blood transfusion with preoperative autologous donation combined with the administration of recombinant human erythropoietin in patients undergoing liver resections. Chan et al.[105] demonstrated that preoperative autologous blood donation in patients with hepatic malignancies did not alter the rate of tumor recurrence or disease-free survival. Some studies examining the use of preoperative autologous blood donation actually resulted in improved prognosis in patients undergoing hepatectomy for hepatocellular carcinoma.[106,107] Autologous blood donation in the context of donor hepatectomy for living donor liver transplantation did not result in any benefits in a study by Jawan et al.[108] In fact, blood transfusion was not needed in the entire group of 84 patients, whether they preoperatively donated blood or not.

The main disadvantage of this method is that autologous donation is more expensive than allogeneic transfusion.

Acute intraoperative normovolemic hemodilution

The goal of acute normovolemic hemodilution (ANH) is to avoid allogeneic blood transfusion. The procedure involves the removal and storage of a calculated volume of autologous blood immediately before the surgery, and simultaneous replacement with crystalloid or colloid fluids. The collected blood is re-infused during surgery after the period of blood loss.

Physiological consequences of acute normovolemic hemodilution include reduction of viscosity of blood (with improvement of microcirculation, reduction of left cardiac afterload and increased cardiac output), peripheral vasodilatation (with reduced peripheral vascular resistance), increasing of central venous and pulmonary capillary wedge pressures (due to increased venous return), and right deviation of the hemoglobin dissociation curve (with better oxygen delivery in the periphery). The main concern in the use of acute normovolemic hemodilution is finding the point of critical oxygen delivery in specific organs. During this procedure, it is crucial to maintain an adequate cardiac output and normal tissue perfusion. The main contraindications for ANH are the presence of cardiac disease, baseline hemoglobin of less than 9 g/dL, and clotting disorders.[109]

The maximum volume to be withdrawn is determined according to estimation of initial blood volume (around 65-70 ml/kg for young adults) and initial and target hemoglobin. Thus, the acceptable volume of blood to be collected could be determined by the formula: $V = EBV \times (H_i - H_f)/H_{av}$, where V is the volume of blood to be withdrawn (in mL), EBV is the estimated blood volume of the patient (in mL), H_i is the initial hematocrit before the procedure, H_f is the target final hematocrit after hemodilution, and H_{av} is the average of the H_i and H_f. Hemodilution can be classified as mild (target hematocrit more than 30%), moderate (target hematocrit 20-30%) or severe (target hematocrit less than 20%).[54]

Usually, the first 450-500 mL of blood can be withdrawn without the need for fluid replacement. After that, blood is replaced with fluid in the ratio of 1 mL of blood: 3 mL of lactate ringer or normal saline. Optionally, 6% hydroxyethel starch or 5% albumin may be used in a 1:1 ratio. Between 2-4 units (approximately 400-500 mL each) of blood can typically be safely removed in most cases. The bags of blood should be kept in the operating theatre. Blood may be kept at room temperature for up to four hours, or at a temperature of 6°C for a longer period of time.

Method of transection

Several modalities and devices have been tested to reduce bleeding from the parenchymal cross section during liver transection. The use of vascular staplers enables simultaneous transection of hepatic parenchyma and vessels. Reddy et al.[110] found a significant reduction in intraoperative blood loss and transfusion requirements using vascular stapling devices. However, other studies have been unable to demonstrate similar results. Also, results comparing the use of radiofrequency, harmonic scalpel, water jet, and ultrasonic devices have been conflicting. Most have been unable to demonstrate superiority of any one technique, and no technique has proven to be preferable to the clamp-crush method to reduce blood loss during hepatectomy.[111–115] Another attempt to reduce cross section bleeding has been through the use of hemostatic topical agents, such as collagens, fibrins, and cyanoacrylate agents; however, there is no evidence that topical agents yield a significant difference in operative blood loss or transfusion requirement.[116–120]

MANAGEMENT OF POST-HEPATECTOMY BLEEDING

Hemorrhage after liver resection usually originates from the liver surface or the diaphragm and occurs within the first 48 hours.[121] Drainage of blood by abdominal drains and/or hemodynamic disturbances (hypotension and/or tachycardia) are indicative of hemorrhage. Loss of blood through abdominal drain does not exclude bleeding, since clots can prevent adequate drainage. Conservative management includes correction of an eventual coagulopathy and blood transfusion. Re-laparotomy is required in 1-8% of cases of postoperative hemorrhage and carries a high mortality rate (17% to 83%). Criteria for laparotomy are variable, but blood loss exceeding 1 L, ongoing need for transfusion, hemoglobin decreasing by 3-4 points requiring transfusion, and hemodynamic instability are reasonable indications.[58,59,121–123]

POSTOPERATIVE LIVER FAILURE

DEFINITION AND PATHOPHYSIOLOGY

After liver resection, there is an expected and limited deterioration of liver function. The ability of the remnant liver to regenerate leads to rapid restoration of liver volume and function, as can be demonstrated by liver function tests and volumetric measurements after major hepatectomy. Severe dysfunction leading to acute liver failure is uncommon, but it is among the most serious complications after hepatectomy because it is associated with a high morbidity and mortality (60% to 100% of all deaths after hepatectomy). Nevertheless, attempts to precisely define this condition are recent and the definition varies among groups, resulting in a widely variable incidence (0-32%) and making comparison of rates challenging.[6,14,17,19,124–131]

The precise pathophysiology of postoperative liver failure (PLF) remains poorly understood, but it occurs when the regenerative capacity of the remnant liver parenchyma is not able to surmount the increased postoperative metabolic demand and preserve or recover an adequate hepatic function. Thus, the **volume** and the **quality of the remnant liver** are some obvious predictors of PLF, relying on the extension of hepatic resection and the presence of underlying chronic liver disease, respectively. Small remnant liver volume may not have enough hepatocytes for adequate minimal liver functions. A damaged remnant liver parenchyma ha a reduced functional and regenerative ability. Cirrhosis, steatosis, and chemotherapy associated liver injury (CALI) are conditions associated with increased risk of mortality after liver resections (most of them for PLF). Indeed, the more the remnant liver parenchyma is injured, the greater the remnant volume that is needed, as discussed in other chapters of this textbook.

Other associated risk factors for PLF include hepatic parenchymal **congestion** (inadequate outflow), prolonged parenchymal **ischemia** (due to vascular clamping, hypotension, and anesthetic drugs, among others), and **ischemia-reperfusion injury** (mainly depending on duration of vascular clamping). A small remnant liver must have an adequate blood inflow and outflow, and biliary drainage. On the other hand, **hyperperfusion** (excessive portal flow to a small volume of hepatic parenchyma) is harmful because it leads to sinusoidal dilatation, hemorrhagic infiltration, centrilobar necrosis and prolonged cholestasis, and further impaired liver function (the so-called "small-for-size" syndrome).[132–134]

Sepsis has also a detrimental effect on liver function and hepatic regeneration; **blood transfusion** increases the risk of sepsis and postoperative liver failure. Occasionally, PLF occurs due to portal or hepatic vein obstruction (thrombosis, torsion, or surgical injury).

Postoperative liver failure leads to an unexpected kinetic of postoperative liver tests. After uncomplicated liver resection, serum bilirubin and INR – well-known measures of hepatic function – should tend to return to normal levels on postoperative day 5, as illustrated in **Figure 1**. Most proposed definitions of PLF in the literature are based on abnormalities of these tests, using various cut-off values at different postoperative time points.

Therefore, the consensus of the International Study Group of Liver Surgery (ISGLS) defines PFL as a "postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which is characterized by an increased international

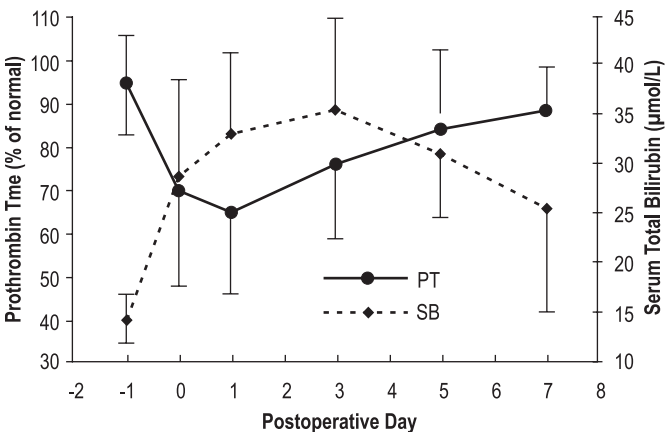

Figure 1. Natural history of two liver function tests (prothrombin time and bilirubin) after liver resection on survival patients. Serum bilirubin tends to return to preoperative levels on postoperative day 5, and prothrombin time usually reaches normal values quickly soon, on postoperative day 3. (Adapted from Balzan et al.[129])

normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5." Attention should be paid to patients with abnormal preoperative liver function tests and those that receive clotting factors, such as fresh frozen plasma (FFP), and/or present postoperative biliary obstruction, both being conditions that affect the expected levels of the evaluated postoperative liver function tests. However, no specific cut-off for these tests is defined and therefore any concomitant abnormality of INR and serum bilirubin is defined as PLF.

The presence of the "50-50" criteria,[129] a combination of prothrombin time index <50% (corresponding usually to a INR>1.7) and serum bilirubin >50 μmol/L (i.e., 2.9 mg/dL), on postoperative day (POD) 5 has been identified as a strong predictor of postoperative mortality and it has been frequently used as definition of PLF. In fact, the presence of the "50-50" criteria on POD 5 is associated with a mortality rate of 59%, as opposed to 1.2% if these criteria are not met. A study by Mullen et al.[13] found that a peak serum bilirubin concentration >7 mg/dL predicted liver-related death in non-cirrhotic patients after major hepatectomy, and this definition has also been used as a means of identifying PLF in non-cirrhotic patients.

The three definitions noted above represent those that are used most worldwide, and were recently compared in a large cohort study.[135] As expected, the ISGLS definition showed the highest sensitivity among the three. However, it was the least relevant in predicting mortality and morbidity (lower specificity and positive predictive value). The positive predictive value for mortality using the ISGLS criteria on POD 5 was only 18.3%, lower than the 47.1% and 40% obtained with the 50-50 and Mullen criteria, respectively. The incidence of PLF in this cohort was 11.6% using the ISGLS definition on POD 10 (and 9% on POD 5), 6.5% using the Mullen criteria, and 3.5% using the 50-50 criteria.

PLF has also been stratified according its severity. Schindl et al.[127] used four parameters (serum bilirubin, prothrombin time, serum lactate, and grade of encephalopathy) in a score to classify PLF into four grades of severity, as shown in **Table 2**. The ISGLS consensus classifies PLF according to its severity into three groups (**Table 3**): **Grade A** does not present specific symptoms, only a deterioration on routine laboratory liver function tests; **Grade B** includes patients that need non-invasive treatments but commonly require

Table 3. Criteria for grading of posthepatectomy liver failure.

	Criteria for **Grade A**	Criteria for **Grade B**	Criteria for **Grade C**
Specific treatment	Not required	- Fresh-frozen plasma - Albumin - Daily diuretics - Noninvasive ventilation - Transfer to intermediate/ intensive care unit	- Transfer to intensive care unit - Circulatory support - Need for glucose infusion - Hemodialysis - Intubation and mechanical ventilation - Extracorporeal liver support - Rescue hepatectomy/liver transplantation
Hepatic function	- Adequate coagulation (INR<1.5) - No neurological symptoms	- Inadequate coagulation (INR ≥1.5 and <2.0 - Beginning of neurologic symptoms	- Inadequate coagulation (INR≥2.0) - Severe neurologic symptoms
Renal function	- Adequate urine output (>0.5 mL/Kg/h) - BUN<150 mg/dL - No symptoms of uremia	- Inadequate urine output (≤0.5mL/Kg/h) - BUN<150 mg/dL - No symptoms of uremia	- Renal dysfunction not manageable with diuretics - BUN≥150 mg/dL
Pulmonary function	- Arterial oxygen saturation >90% - May have oxygen supply via nasal cannula or oxygen mask	- Arterial oxygen saturation <90% despite oxygen supply via nasal cannula or oxygen mask	- Severe refractory hypoxemia (arterial oxygen saturation ≤85% with high fraction of inspired oxygen)
Additional evaluation	Not required	- Abdominal ultrasonography/CT - Chest radiography - Sputum, blood, urine cultures - Brain CT	- Abdominal ultrasonography/CT - Chest radiography/CT - Sputum, blood, urine cultures - Brain CT - ICP monitoring device

The patient's posthepatectomy liver failure is graded by the worst idenfied criteria.
BUN: blood urea nitrogen; CT: computed tomography; ICP: intracranial pressure. (Adapted from Rahbari et al.[136])

additional diagnostic evaluation; and **Grade C** patients require invasive methods for management, and present symptoms such as ascites, hemodynamic instability, respiratory failure, and encephalopathy. Rahbari et al.[136] evaluated the clinical applicability of the ISGLS definition and grading in 835 patients, and found an incidence of 1%, 8%, and 2%, and mortality rate of 0%, 12%, and 54%, for PLF Grades A, B, and C, respectively.

RISK FACTORS

Clinical factors associated with the above-mentioned pathophysiological mechanisms and predictive of increased risk of PLF can be grouped as patient-related, surgery-related, and postoperative causes. These factors are summarized in **Table 4**.[137]

Underlying chronic liver disease increases the risk of PLF. Parenchymal injury from any etiology represents a potential risk factor for postoperative liver dysfunction. Hepatocyte damage leads to variable degrees of hepatic dysfunction, and preoperative evaluation is challenging. Chemotherapy-associated liver injury (CALI), such as that due to irinotecan and oxaliplatin, and cirrhosis of any etiology, are well-established risk factors for PLF. Moderate steatosis represents a risk factor for PLF.[138]

Diabetes, malnutrition, renal insufficiency, obesity, active viral hepatitis, and advanced age have also been reported as risk factors for PLF, likely associated with alterations in liver metabolism, immune dysfunction, and hepatic steatosis.[2,8,130,139–143] Surgery-related risk factors for PLF are mainly associated with a small remnant liver, ischemia, and bleeding.[144,145] In a group of non-cirrhotic patients, Schindl et al.[127] found an incidence of severe PLF of 0%, 9%, and 30% after minor resection, standard major resection, and extended major resection, respectively.

Large volume of estimated blood loss, intraoperative transfusion requirement, and need for vascular resection are associated with PLF.[121,129,146–149] Excessive blood loss might induce bacterial translocation and systemic inflammation, and blood transfusions exert an immunosuppressive effect. Thus, blood loss of more than 1000-1250 mL represents a risk factor for infection and PLF.[2,17,50,150,151] Postoperatively, hemorrhage and infection seem to increase the risk of PLF.[2,142]

Table 4. Risk factors for postoperative liver failure.

Patient related	-Diabetes mellitus -Obesity -CASH -Hepatitis B, C -Malnutrition -Renal insufficiency -Hyperbilirubinemia -Thrombocytopenia -Lung disease -Cirrhosis -Age >65 years
Surgery related	-EBL >1,200 mL -Intraoperative transfusions -Need for vascular resection -Major hepatectomy -Skeletonization of hepatoduodenal ligament -Future remnant liver <25%
Postoperative management	-Postoperative hemorrhage -Intra-abdominal infection

EBL: estimated blood loss; CASH: chemotherapy-associated steatohepatitis. (Adapted from Kauffmann and Fong[137])

PREVENTION

Prevention and/or treatment of the causes of PLF should minimize its incidence. First, careful selection of patients and procedures can help prevent insufficient residual functional liver parenchyma. It is crucial to planned hepatic resection to enable sufficient remnant liver volume, which has a correlation with the quality of remnant liver parenchyma.

The safe volume of remnant liver has been widely investigated, and this topic is discussed in detail in other chapters of this textbook. In brief, it has been established that a remnant liver volume of 20-25% of the total functional liver volume (excluding tumor volume) or a remnant liver volume-to-body weight ratio (RLV-BWR) of more than 0.5% of the body weight in an otherwise healthy liver is sufficient.[144,145] When a chronic underlying liver disease such as hepatitis or chemotherapy-associated liver injury is present, this limit should be 30-40%; if cirrhosis is present, a RLV-BWR of more than 1.4% should be reached in Child A patients.[152] Child B and C patients tolerate only minor or no resection, respectively.[17,153,154]

Aside from the preoperative estimation of remnant liver volume by radiological methods, other techniques have been evaluated to estimate hepatic function, mainly in cirrhotic patients. Some of these techniques are discussed in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection).

Patients preoperatively identified as being at high risk for PLF due to an insufficient future remnant liver could benefit from techniques to increase the remnant parenchyma, such as by portal vein embolization (PVE). Preoperative PVE of the hepatic segments to be resected induces a hypertrophy of the remnant segments and prevents an acute increase of the portal vein pressure at the time of resection. A degree of hypertrophy of more than 5% after three to four weeks of PVE is associated with improved outcomes after liver resection.[155–158] This topic is described in more detail in **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization

and Local Ablation of Hepatic Tumors).

If the remnant liver is small, with a risk of small-for-size syndrome (usually less than 0.6% of body weight for major resections and less than 0.8% for partial liver transplantation), portal pressure can be reduced by ligature of the splenic artery.

Ischemia-reperfusion injury following prolonged vascular occlusion can be prevented by liver preconditioning (ischemic or pharmacological).[159–162] Ischemic preconditioning is the most used method and consists of a brief period of hepatic ischemia, usually 10 minutes, followed by a period of reperfusion before a prolonged period of vascular clamping.[163]

Intraoperative strategies to minimize blood loss include use of low central venous pressure, vascular clamping (preferably intermittent to avoid prolonged periods of hepatic ischemia), and hemostatic agents and surgical devices. Avoiding blood loss and blood transfusion should reduce the risk of postoperative liver failure.

Finally, venous drainage of the remnant liver should be optimized. Hepatic congestion could lead to bleeding in the cut surface, liver dysfunction, and impaired capacity of regeneration of the congested segments.[164] Adequate knowledge of the venous system anatomy, venous reconstruction when necessary, and fixation of the remnant liver in its anatomical position are measures to prevent congestion and liver failure.[165]

MANAGEMENT

Early detection of PLF is crucial to its management. Monitoring liver function by routine biochemical liver function tests is essential to recognize and predict PLF, as proposed with the ISGLS criteria and the 50-50 criteria. Severe PLF can lead to multiple organ failure and death. Clinical manifestations include potentially lethal renal failure due to relative hypovolemia and severe renal vasoconstriction leading to acute tubular necrosis, hepatic encephalopathy (from asterixis up to coma), ventilatory dysfunction due to arterio-venous shunt, hyperbilirubinemia, coagulopathy, and postoperative systemic inflammatory response syndrome. Reduced peripheral vascular resistance can lead to hemodynamic instability. Renal failure contributes to azotemia, ascites, and hepatic encephalopathy. Also, PLF increases susceptibility to serial complications, mainly infectious. Sepsis can occur secondary to PLF or aggravate it.[166–168]

Supportive therapy for system failures may require mechanical ventilation, vasopressor therapy, fresh frozen plasma, blood transfusion, artificial nutrition, and substitutive renal therapy.

Reversible causes of PLF should be promptly identified and treated. Vascular disorders – such as portal, arterial, or hepatic thrombosis – are usually recognized by Doppler ultrasound. Management of portal vein thrombosis and/or venous outflow obstruction is somewhat controversial. Surgical and endovascular approach are possible. Postoperative small-for-size syndrome may be managed by percutaneous splenic artery embolization or with the use of β-blockers or analogues of somatostatin.

Systematic use of antibiotic therapy should be initiated early, since sepsis is a common event leading to death in the context of PLF.[169,170] Cultures for bacteria and fungi should be performed frequently to guide treatment.

Optimal and early therapy for PLF may control metabolic requirements and restore homeostasis and the capacity of the liver to regenerate. If conservative management fails, liver transplantation may be proposed if there is no contraindication.[171] Most patients submitted to liver resection for secondary liver metastases are not good candidates for liver transplantation; however, those undergoing resection of primary tumors with favorable tumor characteristics could be eligible for emergency liver transplantation.[171,172]

Extracorporeal liver support devices (such as MARS® [molecular adsorbent recirculating system] and Prometheus®) using albumin-linked hemodialysis systems, and bioartificial liver-supporting systems using xenogeneic or human hepatocytes, have been tested for acute liver failure.[173,174] These systems lead to biochemical improvements but poor clinical outcomes. They could be used as a bridge for liver transplantation.

Chronic hepatic liver failure is rare, but can occur in cirrhotic patients with very limited ability for hepatic regeneration.

BILE LEAK

DEFINITIONS AND CLASSIFICATION

Bile leak is the most common biliary complication after a hepatectomy, occurring in 0.4% to 33% of cases.[7,17,175–187] Despite a decrease in mortality and other complications after hepatectomy, incidence of bile leak remains an important concern. In fact, a recent study including 2,628 liver resections even demonstrated a rising incidence of bile leak: from 3.7% in the early period of the study to 5.9% in the later period.[184]

The variability in the reported rate of bile leak after hepatectomy may partly be due to differences in definitions. The International Study Group for Liver Surgery (ISGLS) has proposed a standardized definition and grading system for bile leakage as outlined in **Table 5**.[188]

A recent study to validate these concepts included close to 1,000 patients, most undergoing liver resection for colorectal liver metastases, and identified an incidence of bile leak of 7.3%.[176] Most frequently, Grade A (3.3%) and Grade B (3.4%) bile leakage were found. Incidence of Grade C was 0.6%.

Bile leakage can also be classified according to its origin. Nagano et al.[181] classified postoperative bile leaks as i) type A, minor leaks from small bile radicles on the surface of the liver; ii) type B, leaks from inadequate closure of the major bile duct branches on the liver's surface; iii) type C, injury to the main duct commonly near the hilum; and iv) type D, leakage due to a transected duct disconnected from the main duct. Others[187] have classified bile leak as peripheral, i.e. that originating from the cut surface of the liver, and central, i.e. that from the extrahepatic bile ducts.

Bile leak can be graded according to the Clavien score for postoperative complications.[189] ISGLS grading of severity correlates with Clavien score.[176]

Bile leaks following liver resections result in increased morbidity (especially intraperitoneal septic complications and liver failure), prolonged intensive care and hospital stay, increased healthcare costs, and increased mortality rates.[22,175,177,190–195]

MANAGEMENT

While many patients with postoperative bile leak do not need any specific treatment, a large proportion require some form of intervention, from conservative procedures to re-laparotomy.

Several studies with large series of liver resections have reported spontaneous bile leaks healing in most patients.[181,185,186] Bile leaks originating from the cut surface of the liver are more prone to close spontaneously than central bile leaks.[181] A drain output of greater than 100 mL/day was identified as a factor for failure of conservative management in a multivariate analysis.[185] The initial management of bile leaks in patients with a preexisting drain is conservative, including prolonged drainage and antibiotics if persistent fever is present. In the initial report of ISGLS about bile leaks, nearly half were Grade A and no additional radiological, endoscopic, or surgical intervention was necessary. This was confirmed in a large multicenter study including almost 1,000 patients, where 45% of bile leaks were Grade A.

Patients without a well-functioning drain can develop intraperitoneal collections and sepsis. Percutaneous drains are usually placed by interventional radiology to treat these complications.

If bile leak is persistent despite adequate drainage, additional biliary drainage is useful to reduce intrabiliary pressure and bile flow out through the injured bile duct, leading to closure of the fistula. Drainage of the biliary tree is usually obtained using endoscopic retrograde cholangiography (ERC), sphincterotomy or stent placement, or percutaneous transhepatic drainage (PTD). After a hepatectomy with preservation of the common bile duct, ERC with stenting, nasobiliary drainage, or sphincterotomy is usually effective to resolve persistent bile leaks. When a hepaticojejunostomy is present (typically after associated bile duct resection), PTD is the best modality of biliary drainage.[196]

More aggressive treatment by laparotomy is reserved for failure of conservative endoscopic or radiological management, and is associated with a high mortality rate.[190] Failure of non-surgical management includes persistent bile leak, biliary peritonitis, and sepsis. Surgical drainage of a bilioma or a bile leak is the most frequent procedure, but in some cases bilioenteric anastomosis or even re-hepatectomy is needed. The frequent presence of adhesions and sepsis makes these procedures more difficult.

A special condition is bile leakage originating from an excluded segment, i.e. a bile duct disconnected from main biliary tree. A typical cause is aberrant biliary anatomy or a non-anatomical resection. Bile leak from a disconnected duct results in persistent bile drainage or recurrent intra-abdominal collection and sepsis. ERC or percutaneous cholangiography usually do not demonstrate any bile leakage; only a fistulogram or percutaneous cholangiography of the involved segmental duct are able to identify the location of the bile leak and the excluded segment. In this setting, endoscopic or percutaneous biliary drainage has no effect. Definitive treatment often requires a bilioenteric anastomosis with the bile duct disconnected, or a resection of the respective hepatic segment.[197–199]

Table 5. ISGLS definition and grading of post-hepatectomy bile leak.

DEFINITION
Bile leak is defined as fluid with an elevated bilirubin level (≥ three times the serum bilirubin level) in the abdominal drain or intra-abdominal fluid on or after postoperative day three or the need for radiological intervention drainage owing to biliary collections or re-laparotomy due to biliary peritonitis.
GRADING
Grade A- Bile leak requiring no or little change in patients' clinical management
Grade B- Bile leak requiring a change in patients' clinical management (such as additional diagnostic or interventional procedures) but manageable without a re-laparotomy. OR: a Grade A bile leak lasting for > 1 week.
Grade C- Bile leak requiring re-laparotomy

ISGLS: International Study Group of Liver Surgery. (Adapted From Koch et al.[188]).

RISK FACTORS

Despite the heterogeneity of definitions for bile leakage, some risk factors are well established in the literature.

Hepaticojejunostomy has been identified as a risk factor for bile leaks (rates from 13.6% to 21% when a hepaticojeunostomy is associated, versus rates from 3.2% to 4.6% in hepatectomy only).[187,200] In fact, complex liver resections have been associated with a higher incidence of postoperative bile leakage.[177] A recent study including more than 2,600 hepatic resections between 1997 and 2011 identified the following independent predictors of bile leak: i) bile duct resection, ii) extended hepatectomy, iii) repeat hepatectomy, iv) en bloc diaphragmatic resection, and v) intraoperative transfusion. The authors report an increase in the incidence of bile leakage in more recent years (from 3.7% to 5.9%), associated with the more frequent performing of complex hepatectomies.[184]

Other studies have identified specific risk factors for bile leakage after hepatectomy, including central bisectionectomy, repeat hepatectomy, a large cut surface area ($\geq$57.5 cm^2), intraoperative blood loss $\geq$775ml,[183] exposure of the major Glisson's sheath,[175,181] resections including segment 4, peripheral cholangiocarcinoma,[179] and long operative time.[201] Most of these factors characterize complex liver resections.

Some procedures, such as surgery for hydatic cysts or polycystic liver disease, are associated with high rates of postoperative bile leakage.[202–204] Biliary strictures previous to hepatectomy can also be responsible for postoperative bile leakage, and can originate from previous surgery, tumor ablative techniques (such as radiofrequency), or intra-arterial chemoembolization. Sadamori et al.[182] suggest latent strictures as the main cause of bile leakage requiring endoscopic or percutaneous treatment after liver resection for hepatocellular carcinoma.

PREVENTION

Despite the use of several strategies reported to prevent bile leak, or to detect and repair it intraoperatively, incidence of postoperative bile leak is still substantial. This is due, at least partially, to greater complexity of liver resections, as described in the section above. However, some points should be kept in mind to avoid this potentially fatal complication.

When a hepatectomy carrying a high risk of postoperative bile leakage (such as major hepatectomies, resections including segment 4 or with major Glisson's sheath exposition, or re-hepatectomy) is contemplated, preoperative assessment of the biliary anatomy should be considered to avoid intraoperative injury of hepatic ducts.[190,201]

Adequate intraoperative identification and closure of small and large bile ducts on the cut surface is crucial to avoid postoperative fistula.

A recent meta-analysis demonstrated a decreased risk of bile leak using a vessel-sealing system when compared with the clamp-crush method.[205] However, published studies are limited and have significant heterogeneity. Thus, considering the scarcity of randomized controlled trials, it is not possible to declare the superiority of one technique among the various techniques for parenchymal cross section.

Besides parenchymal transection, intraoperative detection and repair of bile leak seems to prevent postoperative fistula. There are many reports of reduction of bile leak after introduction of intraoperative detection tests.[175,187,206]

Various methods to identify bile leaks after parenchymal transection can be applied, and any detected bile leak point should be sutured. An easy method is the application of white gauze on the transection surface and verification of bile-tainted areas. The "white test" is a largely used tool with promising results in intraoperative detection and prevention of postoperative bile leak. A fatty emulsion is injected (usually in the cystic duct) and any extravasation detected is adequately sutured. The advantage of this tool is that the test can be repeated without contamination of the resection surface, because the fatty emulsion can easily be washed away with saline without leaving any color behind.[207–211] A prospective study including 137 patients validated the white test and found a postoperative bile leakage rate of 23% in the control group versus only 5.3% of tested patients ($P<0.01$).[208]

Other methods include the injection of solutions or air (air leak test) into the main biliary tract, usually by a catheter inserted through the cystic duct. Recent studies have demonstrated an increase in intraoperative detection of bile leaks and reduction of postoperative bile leak.[212] While the only randomized trial that assessed the efficacy of bile leak testing using saline[195] found a similar incidence of bile leaks in both the test group and the control group (6% vs. 4%, respectively) after liver resections, another series demonstrated a reduction of postoperative bile leaks. Zimmitti et al.[212] reported a rate of postoperative bile leak of only 1.9% when the air leak test was used, against a rate of 10.8% when the test was not performed. The test allowed for identification of uncontrolled bile ducts in 62.1% of patients. Yamashita et al.[175] reported no bile leaks in 102 consecutive liver resections after they started using intraoperative testing with transcystic saline injection. Before using the test, the rate of postoperative bile leak was 4.5% in 679 hepatectomies. Lam et al.[213] evaluated a test with injection of methylene blue and found a reduction in the incidence of postoperative biliary fistulae. Other recent studies[206,214] have reported a reduction of postoperative bile leaks with the use of a leak test with indocyanine green (ICG) fluorescent cholangiography. Kaibori et al.[206] identified postoperative bile leaks in 10% of the control group (conventional ICG test group) versus no bile leaks when ICG with PDE was used ($P<0.05$). Similarly, Near Infrared Imaging (NIR) has also

been used for intraoperative identification of bile leaks;[215] however, these recent techniques require equipment that is not widely available.

There is actually no consensus concerning the use of intraoperative tests for preventing bile leakage, but evidence suggests that classical cholangiography and injection of methylene blue are not useful for this purpose. Also, most studies are with a small number of patients and in single institutions without external validation.

The value of fibrin glue or other topical sealant application to reduce bile leakages has not yet been properly appraised.[216] Despite some studies suggesting a beneficial effect,[179,217] two randomized trials including 300 and 310 patients found similar incidence of postoperative bile leaks with the use of fibrin sealant and in controls (10% vs. 11% and 14% vs. 14%).[119,218]

The use of omental wrapping after hepatic resection is supposed to reduce the incidence of bile leakage; however, a recent retrospective study showed no differences with this technique.[219]

OTHER COMPLICATIONS

SURGICAL SITE INFECTION AND SEPSIS

Surgical site infection (SSI) is the most common nosocomial infection in surgical patients, accounting for 38% of all such infections. SSI after liver resection occurs in 3% to 21% of cases[3,182,220–224] and is associated with increased postoperative liver failure and mortality.[220]

The main risk factors associated with this complication are postoperative bile leak, preoperative biliary drainage, the presence of infected bile, repeat hepatectomy, inadequate postoperative glycemic control, obesity, excessive blood loss, major hepatectomy, and the presence of multiple comorbidities.[182,222–226]

A large study using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database and including 2,332 patients found pre-operative open wound, hypernatremia, hypoalbuminemia, elevated serum bilirubin, dialysis, and longer operative time as predictors of SSI.[221]

Three recent studies[182,220,222] evaluating SSI after HCC resection identified bile leak as a risk factor for organ/space SSI, which is more frequent than wound SSI. Incidence of SSI varied from 14% to 21%, and in one study it was associated with increased mortality (11% vs. 0.7%). Beyond bile leak, other risk factors for SSI were blood loss, prolonged surgery, and re-hepatectomy.

A Japanese study[226] suggested the presence of positive bile culture as a risk factor for SSI. They found bile culture positives in 83%, 8%, and 10% of patients operated on for hepatolithiasis, HCC, and colorectal liver metastasis, respectively.

Thus, avoiding postoperative bile leakage and reducing blood loss are potential strategies to reduce infectious complications after liver resections. Rigorous postoperative glycemic control is essential, and early recognition of postoperative infection as well as prompt administration of broad-spectrum antibiotics is crucial. Delayed antibiotic therapy was associated with increased infectious mortality in one study.[223] However, there is no evidence that routine use of postoperative systemic antibiotics reduces postoperative infective complications.[227] Also, the use of routine drainage after liver resection is considered controversial.[228–230] Usually, routine drainage is not recommended in patients with chronic underlying liver disease, and is recommended for patients with high risk of postoperative bile leak (such as in the case of hepaticojejunostomy). For the other patients, there is no strong evidence of advantages using routine drainage.

The evidence that disruption of gut barrier function and intestinal bacterial overgrowth can promote bacterial translocation and infectious complications[231,232] has led to the use of early enteral nutrition and symbiotic treatment as promising approaches. Symbiotic treatment is a combination of prebiotics (non-digestive food that alters the growth and activity of colonic flora) and probiotics (viable bacteria that improve the intestinal microbial balance) that reduces the rate of infectious complications after hepatobiliary surgery.[233,234]

Postoperative sepsis and liver failure are serious complications after liver resection that present a potent combined effect. Postoperative liver failure leads to a global suppression of the immune system. The reduced ability of Kupffer cells to eliminate pro-inflammatory mediators, bacteria, and bacterial products leads to an amplified inflammatory response. In another sense, the sepsis per se aggravates the liver dysfunction.[235]

Transitory liver dysfunction after major hepatic resection challenges the diagnosis of sepsis, since the typical picture of fever and leukocytosis may not be present and hyperbilirubinemia and encephalopathy may be due to the liver failure.[236]

Diabetes mellitus represents a higher risk of sepsis after hepatectomy for hepatocellular carcinoma.[237]

In most cases digestive bacteria are involved, but other aerobic and anaerobic bacteria and fungi may be at the origin of sepsis. Polymicrobial infection occurs predominantly when preoperative biliary drainage, prolonged sepsis, and previous use of antibiotic therapy is present.[223]

RESPIRATORY COMPLICATIONS

Incidence of respiratory complications after upper abdomen surgery varies between 7.5% and 80%, depending on the

definition applied.[238–240] After liver resection, pneumonia and pleural effusion are common complications, occurring in approximately 1.9-13% and 5-40%, respectively.[2,3,14] Pulmonary embolism is a less common complication (incidence less than 3%), although rates of up to 10% have been reported after living-liver donation.[3,241]

Diabetes and blood transfusion have been identified as independent risk factors for pneumonia after hepatectomy. Also, prolonged operative time and the use of nasogastric decompression are related to respiratory infection. Transverse subcostal bilateral incision, right liver resections, neoadjuvant chemotherapy, and prolonged surgery are associated with increased risk of pleural effusion. Chemotherapy-associated liver injury has been associated with increased postoperative morbidity.[240] Major resection of a non-cirrhotic liver has been identified as a risk factor for pulmonary embolism. Thrombosis of the hepatic veins is a potential source of pulmonary embolisms.[242,243] It is worth noting that a prolonged prothrombin time is not a protective factor, and thromboembolic prophylaxis should be used even in patients with a prothrombin time less than 50%.

Measures that possibly prevent respiratory complications include strict intraoperative glycemic control, periodic intraoperative reinjection of antibiotics, minimizing blood loss, use of thromboembolic prophylaxis with low-molecular-weight heparin, optimization of postoperative pain control, and use of postoperative noninvasive continuous positive airway pressure. Also, avoiding bi-subcostal incision and the use of nasogastric tubes should be helpful.[240]

RENAL FAILURE

Acute renal failure after large hepatectomies is the most serious postoperative renal complication. Its incidence may reach 15%, and some known risk factors are cardiovascular disease, elevated alanine aminotransferase (ALT), underlying renal disease, and diabetes mellitus.[237,244] The use of low central venous pressure (CVP) does not seem to increase the risk of renal failure. In fact, the incidence of renal failure attributable to a low CVP approach has not been demonstrated.[87] The precise mechanism of liver failure after hepatectomy is unknown. Acute tubular necrosis and hepatorenal syndrome may be responsible for postoperative renal dysfunction.

Hepatorenal syndrome occurs mainly in patients with cirrhosis, and it is characterized by oliguria and a low urine sodium concentration. Perioperative intravascular volume depletion can lead to renal ischemia and precipitate hepatorenal syndrome.

Rehydration and diuretics are usually sufficient to revert mild acute renal failure. Mannitol and hemodialysis can be necessary if severe renal dysfunction occurs.

PORTAL VEIN THROMBOSIS

Portal vein thrombosis (PVT) after liver resection is rarely reported, and most of the literature on postoperative PVT is on liver transplantation, where vascular complications are more frequent. However, the increasing extent of liver resections, mainly with associated vascular clamping, resection and reconstruction, has made this complication more frequent. Yoshiya et al. reported an incidence of 9.1% of PVT after hepatectomy, but most cases were peripheral (63%).[245]

Clinical manifestations of PVT after liver resection are variable. Abdominal pain, nausea, vomiting, anorexia, weight loss, diarrhea, and abdominal distention can be related to bowel congestion or ischemia and ascites. Esophageal varices, splenomegaly, hemorrhage, and cavernous transformation may be present due to the development of portal hypertension and collateral circulation. PVT may remain unrecognized due to the lack of specific symptoms.

Diagnosis is usually made by contrast-enhanced computed tomography (CT), which offers higher accuracy than color Doppler ultrasonography.

Risk factors are based on Virchow's triad (venous stasis, hypercoagulable state, and endothelial injury). Thus, portal vein reconstruction, prolonged Pringle maneuver, small remnant liver volume (probably due to increase in von Willebrand factor/ADAMTS13 ration), and cirrhosis probably increase the risk of PVT.[246]

PVT results in delayed recovery of liver function and delayed liver regeneration.[245] Complete portal vein occlusion and extension of PVT to superior mesenteric vein may result in mesenteric ischemia, sepsis, and death.

Although spontaneous resolution of PVT is not uncommon, anticoagulation therapy should be initiated immediately after diagnosis, if no contraindication is present, in order to limit the propagation of thrombus. If re-canalization does not occur with systemic anticoagulation, site-directed thrombolytics can be used, resulting in high rates of recanalization and low incidence of re-thrombosis. Surgery is required in cases of bowel ischemia.[247]

ASCITES

Ascites is one of the most common complications after resection of hepatic hepatocellular carcinoma, especially due to the presence of cirrhosis. Rates of postoperative ascites vary from 5% to 56%[28–30,248] and can lead to liver failure, early recurrence of hepatocellular carcinoma, and death.[249,250]

Definition of postoperative ascites is variable, but the most accepted is drainage of more than 10 mL/Kg/day. Many factors associated with a high risk of postoperative ascites include: impaired liver function, portal hypertension, small remnant liver, substantial blood loss, and blood

transfusion.[251–253] Cirrhotic patients with preoperative renal dysfunction that undergo liver resection for hepatocellular carcinoma are at risk of massive postoperative ascites and pleural effusion.[252]

Measures such as those to minimizing bleeding and transfusion during liver resection seem to reduce the occurrence of postoperative ascites.

Management of postoperative ascites includes the use of diuretic agents, which is sufficient in most cases. Albumin or fresh frozen plasma can also be used to maintain circulating plasma volume and osmolality. However, even liver transplantation may be necessary in cases of intractable ascites.

A special group of patients at risk for ascites is that undergoing liver resections for polycystic disease, in which ascites can occur in up to 42%. [254] Extensive resection with remnant liver volume less than 30% and the presence of fibrosis are associated with persistent and massive ascites.

SUGGESTED READING

Clavien, P. A. *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann. Surg.* **250**, 187–196 (2009).

This large study consolidates the applicability of the morbidity classification proposed by the authors. Clinical scenarios were evaluated by different centers worldwide and a high degree of agreement was observed.

Stockmann, M. *et al.* The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB (Oxford).* **12**, 139–146 (2010).

This study correlates the LiMAx test with perioperative liver function and a decision tree algorithm is proposed based on this test.

Rahbari, N. N. *et al.* Post-hepatectomy haemorrhage: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB* **13**, 528–535 (2011).

Proposal of a standardized definition and grading for post-hepatectomy hemorrhage, aiming for valid comparison among different studies and centers.

Balzan, S. *et al.* The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann. Surg.* **242**, 824–828 (2005).

This large cohort outlines an accurate and easily applicable definition for postoperative liver failure, based on postoperative bilirubin and prothrombin time. The proposed definition has been largerly used worldwide.

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