

Notes

Risk factors, occurrence, and management of liver failure after hepatic resection

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Liver surgery is considered highly intricate among surgical procedures due to its substantial risks and potential for complications. Liver failure after hepatic resection, a severe complication occurring in approximately 8-10% of patients undergoing significant liver surgery, stands as the primary cause of morbidity and mortality. Appropriate surgical techniques and intensive care management are important in preventing. This study outlines risk factors, occurrence, prevention and management of liver failure after hepatic surgery.

Keywords: Future liver remnant (FLR), Liver dysfunction, Liver resection, Intensive care management, Portal vein embolization (PVE), Post operative care

Sometimes, after significant surgery, there may be mild liver issues, though acute liver failure is infrequent. Those most prone to experiencing postoperative liver failure are individuals undergoing liver resection, with a risk that can reach up to 30%¹. The death rate following a liver resection ranges from approximately 2% for colorectal metastases to around 10% for biliary tumors and hepatocellular carcinomas. However, certain older studies have documented significantly higher mortality rates, reaching up to 30% for extensive liver resections involving more than four segments^{2,3}. Non-fatal complications following liver resections are commonly observed in as many as 45% of cases, ranging from minor occurrences to severe complications such as infections or sepsis, bleeding, leakage, or cardiopulmonary events⁴. Liver failure after hepatic resection is a concerning and severe complication following liver resection, with a higher occurrence rate after resection for hepatocellular carcinoma

(HCC) and hilar cholangiocarcinoma compared to liver resection for colorectal liver metastases (CRLM)⁴, leading to increased illness and death rates.

Liver dysfunction following hepatic resection ranges from a temporary elevation in liver enzymes to severe liver failure leading to death. This spectrum of dysfunction is characterized by coagulopathy, elevated bilirubin levels, encephalopathy, and the subsequent failure of multiple organs. The most effective strategy to mitigate the impact of this complication is to prevent its occurrence through careful and deliberate measures. Identifying patients at risk early on and promptly and appropriately managing those who develop acute liver failure are crucial steps in this process⁵. This study briefly explains the occurrence, risk factors, and management of liver failure after hepatic resection.

Definition

The postoperative liver failure lacks a universally agreed-upon definition, given its potential seriousness, making it challenging to accurately assess its frequency. The International Study Group of Liver Surgery (ILSGLS) has recently formulated a definition: A postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which is characterised by an increased international normalised ratio (INR) and concomitant hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT), increased serum lactate, and hepatic encephalopathy during the postoperative period⁶ (Table 1). The definition by this group in 2011 is widely accepted as a standard to describe the liver failure after hepatic resection.

Occurrence

The occurrence of acute liver failure after hepatic resection has been documented as reaching up to 34% by certain researchers, while others estimate it to be

Table 1 — Severity of postoperative hepatic dysfunction score

Points	0	1	2
Total serum bilirubin ($\mu\text{mol/L}$)	≤ 20	21-60	>60
Prothrombin time (sec. 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

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closer to 8-12%⁷. Schindl *et al.*⁸ argue that the risk should be stated as less than 1% in patients without parenchymal disease undergoing small resections; 10% for those undergoing resections of four segments, and 30% for individuals having five or more segments resected. The significant variance in incidence rates may be attributed in part to the utilization of diverse definitions of liver failure after hepatic resection, but it is also likely influenced by differences in the scope of liver surgery and the patient demographics encompassed in the reported studies.

Causes of liver failure after hepatic resection

Liver dysfunction can arise sporadically following any significant surgical procedure. Instances of intraoperative hypoxia, hypotension, blood transfusion, or sepsis can lead to liver ischemia and/or cellular dysfunction. After liver resection, intraoperative blood loss exceeding one liter requiring transfusion heightens the likelihood of postoperative liver failure and sepsis⁹. Sepsis detrimentally impacts liver function by impeding Kupffer cell function and hinders hepatic cell regeneration¹⁰.

The primary risk factors for postoperative liver failure include (i) the extent of resection; (ii) presence of preoperative liver parenchymal disease (such as cirrhosis); and (iii) hepatic ischemia/reperfusion injury¹¹.

The extraction of four or more segments (out of eight) correlates with a heightened likelihood of postoperative liver failure. When the liver remnant is insufficiently sized, there might not be an adequate number of functioning hepatocytes for proper synthesis, excretion, and detoxification. Additionally, a concern with small liver remnants is hyperperfusion; the relative escalation in blood flow induces sinusoidal dilatation, hemorrhagic infiltration, centrilobar necrosis, and prolonged cholestasis, consequently exacerbating impaired synthetic function and inhibiting cell proliferation¹².

Underlying liver disease diminishes both the functional and regenerative abilities of the liver, rendering it more susceptible to damage. A larger residual volume of the liver needs to remain after surgery to ensure optimal outcomes¹³. Moreover, chemotherapy impacts liver tissue and diminishes its regenerative potential. A recent study from France investigated 101 patients who underwent intensive chemotherapy (≥ 6 cycles of newer agents such as

oxaliplatin and irinotecan) before liver resection. Histological analysis revealed that 50% of patients developed sinusoidal obstruction syndrome, while 10% exhibited steatohepatitis (with 5% displaying both conditions)¹⁴. Both sinusoidal injury and steatosis resulting from chemotherapy impede the regenerative capacity of the remaining liver, thus elevating the risk of postoperative failure^{15,16}. Sinusoidal injury may also arise from "small-for-size syndrome", occurring when dysfunction emerges after a partial graft from a living donor. This phenomenon is believed to stem from portal hyperperfusion of the graft, along with inadequate venous outflow, leading to sinusoidal congestion and endothelial dysfunction¹⁷.

Several patient-related factors such as Diabetes mellitus, Obesity, Chemotherapy-associated steatohepatitis, Hepatitis B, C, Malnutrition, Renal insufficiency, Hyperbilirubinemia, Thrombocytopenia, Lung disease, Cirrhosis, Age >65 years, are linked to an elevated risk of liver failure after hepatic resection¹⁸. Research has indicated that operative mortality rates are higher in individuals with diabetes undergoing curative-intent hepatic resection for colorectal metastases compared to their counterparts without diabetes. In one study, operative mortality stood at 8% among diabetic patients, in contrast to 2% among non-diabetic patients ($P < 0.02$). Moreover, a significant portion (8%) of perioperative deaths in diabetic individuals were attributed to liver failure after resection. The increased mortality observed in diabetic patients undergoing major hepatic resection likely stems from multiple factors, including alterations in liver metabolism, compromised immune function, and the presence of hepatic steatosis, all of which contribute to postoperative liver dysfunction¹⁹.

Prevention

Preventing liver failure after hepatic resection is paramount in its management. For patients identified as high-risk based on preoperative assessment of underlying factors such as cirrhosis, preoperative laboratory values, the volume of liver to be resected, or estimated functional liver volume after resection, strategies should be considered to mitigate the risk of liver failure after hepatic resection. One such strategy is portal vein embolization (PVE), which manipulates portal blood flow by embolizing portal branches in the liver slated for resection. This redirection of blood

flow stimulates hypertrophy of the intended remnant liver before major hepatectomy, thus reducing the risk of liver failure after hepatic resection, even in cases of extended liver resection^{20,21}. Moreover, preoperative PVE reduces intraoperative hepatocyte injury that may result from a sudden increase in portal venous pressure during resection.

Current guidelines recommend PVE for patients with underlying cirrhosis and an anticipated future liver remnant (FLR) of $\leq 40\%$, or for patients with normal liver function and an intended FLR of $< 20\%$. This procedure can be performed with minimal morbidity and mortality and enhances the safety of extended hepatectomies.

Even when neoadjuvant chemotherapy is administered concurrently, PVE induces sufficient hepatic hypertrophy to facilitate major liver resection. CT volumetry should be conducted 3-4 weeks after PVE to evaluate the degree of hypertrophy²², with a hypertrophy degree exceeding 5% correlating with improved patient outcomes (Fig. 1)²³.

Accessing the portal system for PVE can be achieved through either a transhepatic contralateral or transhepatic ipsilateral approach. The transhepatic contralateral approach involves accessing the portal system through the intended future liver remnant (FLR) and is technically simpler than the ipsilateral approach, albeit with a risk of injury to the FLR²⁴. However, accessing segment 4 for embolization becomes technically challenging with a contralateral approach. On the other hand, the transhepatic ipsilateral approach avoids potential injury to the FLR, but acute angulations of the portal branches may pose technical difficulties²⁴. If an extended right hepatectomy is planned, embolization of segment 4 could be prioritized to reduce the risk of embolic

substance dislodgement to the left liver during catheter manipulation.

Since PVE may not always be technically feasible, and disease progression might occur during the waiting period between PVE and surgery, some advocate for the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure, especially for patients requiring trisectionectomy for bilateral liver metastases or intrahepatic cholangiocarcinoma. In ALPPS, blood supply to segments 4-8 is reduced by ligation of the right portal vein branch, combined with parenchymal transection along the falciform ligament^{25,26}. This technique has demonstrated a 74% increase in the FLR volume but is associated with high postoperative morbidity (68%) and mortality (12%)²⁷. While promising results have been observed in small series, with rapid liver hypertrophy and FLR enlargement, further investigation is needed to refine its indications and determine its role in minimizing the risk of liver failure after hepatic resection.

Beyond preoperative techniques aimed at enlarging the FLR, meticulous intraoperative technique and thorough postoperative management significantly contribute to mitigating the risk of liver failure after hepatic resection (Table 2).

In cases of extensive disease burden in the liver, where resection of all lesions would result in an FLR too small to avoid liver failure after hepatic resection, a combination of resection and ablation may be employed to minimize the amount of liver tissue removed. Additionally, wedge resections with minimal tumor-free margins may be utilized to manage multifocal disease, leaving adequate liver tissue intact to prevent liver failure after hepatic resection.

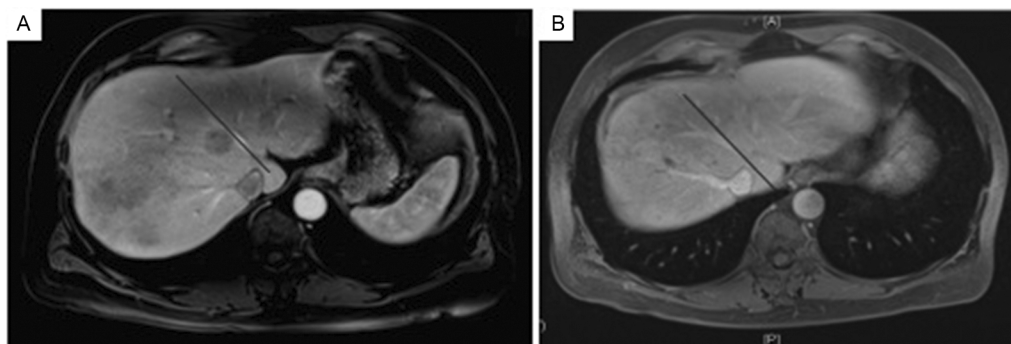


Fig. 1 — (A) Pre-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver; and (B) six weeks post-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver. Line marks middle hepatic vein, dividing right and left hemilivers

Table 2 — Techniques for preventing and minimizing the risk of liver failure after hepatic resection

Period	Techniques
Pre-operative	Weight loss in obese patients
	Nutritional supplementation
	Aggressive management of co-morbid conditions
Intra-operative	Portal vein embolization to enlarge FLR
	Avoidance of skeletonization of hepatoduodenal ligament unless required for R0 resection
	Minimize EBL (resection under low CVP conditions)
	Avoidance of blood transfusions if able
	Close attention to hemostasis to avoid post-operative hemorrhage
Post-operative	Early recognition and treatment of post-op hemorrhage
	Early recognition and treatment of biliary obstruction or leak
	Early recognition and treatment of intra-abdominal infection

Choosing anaesthetic agents

Volatile anaesthetic agents metabolized in the liver are recognized for their capacity to modify hepatic blood flow and trigger temporary alterations in liver enzyme levels. The utilization of halothane, which, upon repeated exposure, may lead to hepatitis (commonly termed 'halothane hepatitis'), has become infrequent. Other volatile agents such as isoflurane, sevoflurane, and desflurane undergo minimal hepatic metabolism, and there is a dearth of evidence indicating hepatotoxic effects²⁸. While some advocate for total intravenous anesthesia (TIVA) as a preferable option in liver surgery²⁹, there is currently no substantiated evidence supporting this claim.

Prevention of blood loss

Postoperative blood transfusions exert an immunosuppressive effect, and as mentioned earlier, the need for blood transfusion following significant blood loss elevates the risk of postoperative liver failure. Techniques aimed at reducing blood loss encompass maintaining a low central venous pressure (<5 mm Hg)³⁰, avoiding excessive positive end-expiratory pressure (PEEP), utilizing thoracic epidurals, furosemide administration, and employing glyceryl trinitrate (GTN) and remifentanyl infusions³¹. Tranexamic acid, an anti-fibrinolytic agent, competitively inhibits the activation of plasminogen to plasmin, thereby mitigating intraoperative blood loss³².

Surgical approaches that minimize blood loss include the utilization of the CUSA™ (Cavitron Ultrasonic Surgical Aspirator), an ultrasonic system employed for liver parenchyma dissection. Operating

at approximately 25 kHz, its ultrasound energy is sufficient to dissect liver tissue without causing damage to vascular structures³³. Hemostatic agents have also proven effective, applied directly onto the liver's cut surface; they contain gelatine matrix granules that facilitate fibrin polymer formation from fibrinogen³⁴. The surgical application of the Pringle maneuver can also prevent blood loss, albeit with the potential risk of inducing ischemic damage.

Management of liver failure after hepatic resection

Liver failure after hepatic resection typically manifests with significantly elevated bilirubin levels compared to other generic causes, serving not only as a diagnostic marker but also holding prognostic relevance³⁵. Any obstructive etiologies contributing to hyperbilirubinemia should be diligently sought out and corrected through radiological or surgical interventions. Occasional compromise to the vascular inflow or outflow of the liver remnant, especially in the early postoperative phase, may result in hepatic ischemia or congestion. The risk of inflow thrombosis escalates in cases where hepatoduodenal ligament skeletonization or vascular reconstruction has been performed³⁶. Additionally, torsion of the left liver remnant following major right resection or skeletonization of hepatic veins can compromise venous outflow, potentially leading to outflow thrombosis³⁷. Diagnosis of these complications can be achieved using bedside Doppler ultrasound, cross-sectional imaging, or definitive angiography.

Hepatic arterial thrombosis, particularly in the post-transplant setting, can result in irreversible hepatic ischemia³⁸. Portal and hepatic venous thrombosis may be managed expectantly with anticoagulation, although thrombectomy or radiological thrombolysis has also demonstrated efficacy³⁹. Postoperative perihepatic collections and abscesses contribute to and exacerbate systemic inflammatory response syndrome (SIRS) and sepsis, necessitating meticulous surveillance and drainage utilizing interventional imaging techniques.

Fluid resuscitation therapy is directed towards achieving optimal tissue perfusion in the presence of excessive capillary leakage. Overreliance on inotropic support can exacerbate hepatic ischemia, as discussed earlier. Decreased systemic vascular resistance results in peripheral pooling, fluid extravasation, and tissue edema.

Acute kidney injury commonly accompanies liver failure following hepatic resection, while excessive fluid administration can induce pulmonary edema and acute respiratory distress syndrome (ARDS)⁴⁰. Impaired renal function prompts an increase in total body water, resulting in electrolyte imbalances like hyponatremia. Administration of diuretics frequently leads to hypokalemia. Furthermore, hyperaldosteronism due to hormonal breakdown failure, uremia associated with renal impairment, and hypophosphatemia linked to hepatic regeneration may contribute to additional electrolyte disturbances. It is imperative to maintain electrolyte balance by strictly adhering to standard replacement protocols.

Pulmonary complications like acute lung injury significantly impact the prognosis of liver failure after hepatic resection in patients. Early intubation and ventilator support, in line with current ARDS guidelines, are recommended. However, prolonged application of elevated positive end-expiratory pressure can exacerbate hepatic congestion, resulting in portal hypertension, ascites development, and impaired liver regeneration.

Neurological complications management

In acute liver failure, the severity of encephalopathy and the extent of cerebral edema are closely intertwined. If cerebral edema is suspected, neuroprotective measures should be initiated, such as controlling carbon dioxide levels and regulating arterial blood pressure⁴¹. Additionally, efforts should be made to maintain blood sugar levels below 10 mmol/L to avoid hypoglycemia, elevate the head by 30 degrees, and refrain from tying the endotracheal tube tightly. While the insertion of an intracranial pressure monitor may provide valuable data, it's important to acknowledge the heightened risks of intracranial bleeding and infection in individuals with liver failure. However, if used judiciously to guide aggressive therapies, such as hypertonic saline administration to achieve sodium levels between 145-155 mmol/L, mannitol administration, cooling to 32-34°C, or deep sedation to induce burst suppression which is beneficial⁴². Alternative monitoring techniques, like transcranial Doppler or jugular bulb oxygen saturation monitoring, may also aid in guiding therapy.

Encephalopathy is typically classified on a scale from 0 to 4 and is reported to stem from the accumulation of various metabolites not effectively cleared by the liver, which typically resolves as liver

function improves. Regular administration of lactulose may prove beneficial⁴³. Seizures should initially be managed with phenytoin and minimal doses of benzodiazepines due to their prolonged action. An electroencephalogram may be necessary to confirm the cessation of seizures if any uncertainty persists. Identifying the underlying cause of the seizures, including brain imaging, is essential for comprehensive management.

Coagulopathy

Coagulopathy is consistently observed in patients with liver failure after hepatic resection and typically manifests subtly, often accompanied by thrombocytopenia, predisposing the patient to hemorrhagic complications⁴⁴. It's widely recognized that persistently low platelet levels are generally well-tolerated, and routine platelet or fresh frozen plasma transfusions are not warranted unless a therapeutic intervention is planned or active bleeding occurs. In addition to coagulopathy, various other factors contribute to an increased risk of gastrointestinal (GI) bleeding, including mechanical ventilation, renal failure, sepsis, and shock. Numerous studies have demonstrated the benefits of stress ulcer prophylaxis using H₂-receptor antagonists (H2RA) or proton pump inhibitors (PPIs); however, mortality rates remain unaffected.

Infection and sepsis

Individuals experiencing liver failure are notably susceptible to developing sepsis, primarily due to a blend of immunosuppression, compromised nutritional status, and heightened gut permeability, which facilitates the translocation of pathogens⁴⁵. Sepsis can emerge from both bacterial and fungal sources. Also, Perihepatic collections and abscesses occurring after surgery contribute to and intensify the systemic inflammatory response syndrome (SIRS). Repeat blood cultures should be obtained to facilitate targeted antimicrobial therapy. SIRS is observed in more than half of patients with acute liver failure (ALF) and is accompanied by both gram-positive and gram-negative bacteremia⁵. Patient outcomes deteriorate with the increasing number of organ system failures, and septic shock in ALF patients is almost always fatal. While there is no established role for postoperative antibiotic prophylaxis following liver resection, it improves outcomes in confirmed ALF cases, and consequently, it is likely beneficial for liver failure after hepatic resection as well. Immediate initiation of broad-

spectrum antibiotic therapy is essential. Fungal infections carry a poorer prognosis compared to bacterial infections, and there may be a potential role for antifungal prophylaxis, although conclusive evidence of its therapeutic efficacy is lacking.

Drug usage management

N-acetylcysteine (NAC) has long been utilized in the management of ALF due to its cytoprotective properties. While it is commonly administered to aid in the recovery from paracetamol overdose, thereby reducing the necessity for liver transplantation, its role in mitigating liver failure after hepatic resection in patients undergoing major liver resection is less well understood. The potential benefit of NAC is grounded in the belief that it exerts a protective effect on the remaining liver tissue by influencing the ischemia-reperfusion injury (IRI) pathway. N-acetylcysteine (NAC) serves as a precursor to glutathione- an antioxidant present in the liver, which plays a vital role in cellular defense mechanisms against oxidative damage caused by free radicals⁴⁶. So, when (NAC) is administered intravenously postoperatively, it helps to mitigate liver dysfunction. NAC also possesses anti-inflammatory properties by inhibiting chemotaxis, thereby reducing the production of oxygen-free radicals by phagocytic cells⁴⁷. Despite the routine postoperative use of NAC in many centers for patients deemed at high risk of developing “Liver Failure after Hepatic Resection”, there is scarce data available to conclusively determine its efficacy or lack thereof.

Liver transplantation stands as the most potent remedy for liver failure after hepatic resection, typically reserved for patients exhausting all other supportive therapies. Initial treatment for liver failure after hepatic resection involves supportive measures targeting failing systems, such as intubation, pressor support, or dialysis. Therapy encompasses albumin, fibrinogen, fresh frozen plasma infusion, blood transfusion, and the commencement of nutritional supplementation.

Intra-hepatic cholestasis, a subtype of liver failure after resection, is characterized by a persistent rise in serum bilirubin without biliary obstruction, while maintaining the liver's synthetic function. A biopsy to confirm this condition should be sought around two weeks post-surgery if diagnosis remains uncertain. Despite optimal supportive care, liver failure after

hepatic resection typically progresses with mortality rates reaching 90%.

Conclusion

Liver failure after hepatic resection remains a significant complication following hepatic resection, occurring in around 8% of patients undergoing major hepatectomy. Its severity spans a spectrum, from mild hepatic insufficiency characterized by temporary hyperbilirubinemia, which typically does not disrupt the anticipated post-operative recovery, to liver failure necessitating intensive care unit management due to multi-system involvement. Various factors contribute to the heightened risk of liver failure after hepatic resection, including obesity, diabetes, prior chemotherapy, underlying cirrhosis, advanced age, male gender, extensive liver resection, and prolonged surgical duration with significant intraoperative blood loss.

Conflict of Interest

Authors declare no competing interests.

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