

Chapter 3

Postoperative Liver Failure

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3.1 Introduction

Technical innovations in surgical techniques, anaesthesia, critical care and a spatial understanding of the intra-hepatic anatomy of the liver, have led to an increasing number of liver resections being performed all over the world. However, the number of complications directly attributed to the procedure and leading to inadequate or poor hepatic functional status in the postoperative period remains a matter of concern. There has always been a problem of arriving at a consensus in the definition of the term: postoperative liver failure (PLF). The burgeoning rate of living donor liver transplants, with lives of perfectly healthy donors involved, has mandated a consensual definition, uniform diagnosis and protocol for management of PLF. The absence of a uniform definition has led to poor comparison among various trials. PLF remains a dreaded complication in resection of the liver, with a reported incidence of up to 8 % [1], and mortality rates of up to 30–70 % have been quoted [2]. Several studies have quoted a lower incidence of PLF in eastern countries, but when it occurs the mortality is as high as in the West [3].

The pathophysiology of PLF remains unclear with most authors presenting clinical conditions which are an overlap of acute liver failure (ALF) and small for size syndrome (SFSS), seen after an inadequate sized liver graft in transplantation. Prevention and treatment strategies also parallel the management of ALF for want of a better understanding of PLF, belying the fact that the former is caused by a toxin or virus and not surgery. The 30-day mortality of PLF is about 25 %, stressing the importance of evaluation of long-term mortality when comparing studies [4].

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In 2005, Balzan et al. [5] published their results of 775 elective liver resections over a span of 5 years. They focussed on serum bilirubin (SB) and prothrombin time (PT) as important prognostic markers of postoperative liver functional status and proposed the '50–50' criteria for the definition of PLF, i.e. the combination of PT >50 % of baseline normal and SB >50 $\mu\text{mol/L}$ on postoperative day (POD) 5 (the '50–50' criteria) was found to be strongly predictive of mortality. The fact that this 'criteria' was a precursor of clinical complications 3–8 days before they appeared lent it a strong base for life-saving interventions. The criticism of this simple calculation has been that it relies only on two laboratory tests and does not factor in the existing clinical status of the patient. The '50–50' rule is limited by the fact that it cannot be applied before POD 5, does not stratify patients and though it predicts death in up to 70 % of patients, it is not based on the clinical severity of the patient.

In 2010, Rahbari et al. [2], of the International Study Group of Liver Surgery (ISGLS) defined PLF as 'a postoperative acquired deterioration' in the functions of the liver: synthetic, excretory and detoxifying. This deterioration is evident by an increase in international normalized ratio (INR) (There may be a need of clotting factors for abnormal INR) and SB, on or after POD 5 (compared with the values of the preceding day). Biliary obstruction needs to be ruled out as a cause for the deranged SB. They also stratified PLF into three grades: A, B and C, depending on up-scaling of the required level of care.

Traditionally, surgeons have resorted to keeping an eye on deteriorating liver function by charting rising INR (coagulopathy), rising SB (hyperbilirubinaemia) and the advent of hepatic encephalopathy (failure of detoxification) as surrogate markers for the functions of the liver. Other scores such as the Child–Pugh score (CTP) and the Model for end stage liver disease (MELD) have also been used by various authors for defining PLF, but a uniform consensus has evaded clinicians due to the multifactorial and diverse aetiology and pathogenesis of PLF.

3.2 Pathophysiology

Following liver resection the patient has multiple pathophysiological mechanisms at work. There is the trauma of surgery, the anaesthetic and haemodynamic changes, the metabolic demands of wound healing and especially in case of the liver: the pathophysiology of ischaemia–reperfusion injury (IRI), liver regeneration and the small for size syndrome (SFSS). Not only do the number of hepatocytes have to be adequate for body homeostasis, they should be functioning optimally and retain their capacity for regeneration. The liver cells suffer mainly from a combination of IRI, hepatic venous congestion and sepsis.

The 'hyperfusion theory' is widely accepted and postulates that the relative spike in sinusoidal perfusion of the decreased cell mass precipitates a vicious cycle. A cascade mechanism of which is a combination of congestion, inflammation, cholestasis and cell death taking place, preventing the normal function of a hepatocyte: uptake, secretion and excretion [6]. In addition cell proliferation and regeneration

are impeded. A standard liver resection for a liver tumour has to deal with IRI, congestion, portal hypertension and sepsis, while, in transplantation denervation and immunosuppression are added as precipitating factors.

IRI persists even after parenchymal damage during liver resection. After a period of ischaemia the inflammatory response in the form of the complement cascade is activated. Activated Kupffer cells generate reactive oxygen species (ROS) which cause endothelial cell damage [7]. Later in the reperfusion phase, these metabolites are swept around leading to a cycle of microvascular injury and microcirculatory changes resulting in apoptosis and cell necrosis with resultant hepatocyte death.

Sepsis may intervene in as high as 50 % of patients after liver resections and may be related to loss of Kupffer cell volume with impaired immune function. The relationship between infection and PLF has not been fully explained [8]. Patients with ALF are particularly prone to developing sepsis. It has been shown that 73 % of patients with PLF develop postoperative sepsis compared with 18 % of patients without [9]. Sepsis has a triad of detrimental effects on liver synthetic function, hepatocyte regeneration and apoptosis by inducing a relative hepatic ischaemia due to systemic hypotension. It induces Kupffer cell dysfunction, releases proinflammatory cytokines, and diminishes detoxification of liver endotoxins thereby leading to diminished hepatocyte proliferation and regeneration [10]. Liver surgery by itself may increase the incidence of infection [8] as major resections are associated with enteric bacterial translocation, which is enhanced by the prolonged inflow clamping and duration of surgery. A major liver resection involving multiple segments significantly impedes the function of the reticuloendothelial system, which is crucial in immune defence against sepsis.

3.3 Precipitating Factors

The precipitating factors for development of PLF can be broadly divided into patient factors, surgery-related factors and postoperative complications and their management (Table 3.1).

Patients with diabetes have a significantly poorer outcome after elective liver resections compared to those who do not have diabetes [11]. Apart from being at higher risk for infections due to decreased immune tolerance, patients with diabetes may also have a higher incidence of fatty liver with insulin resistance and concomitant poorer functional reserve. Preoperative diabetes mellitus is also an independent predictor of 90-day mortality [12].

Patients with cholangitis and active viral hepatitis also do poorly after surgery. In a study, mortality was significantly higher in patients who had resection of hepatocellular carcinoma (HCC) in cirrhosis associated with active hepatitis (8.7 versus 1.5 %; $p < 0.05$) [13]. However, increased risk of PLF with raised SB has been controversial [14]. Cherqui et al. showed that patients with a raised SB level had a morbidity rate of 50 % compared to 15 % in patients with normal SB ($p < 0.01$). However, the incidence of PLF or mortality did not rise when compared with matched controls [14].

Table 3.1 Precipitating factors for postoperative liver failure

Patient factors	Surgery related factors	Postoperative factors
Diabetes mellitus	Estimated blood loss >1200 ml	Postoperative haemorrhage
Obesity	Intraoperative transfusions	Intra-abdominal infection
Chemotherapy-associated steatohepatitis	Need for vascular resection	
Hepatitis B, C	Multisegment resection or major hepatectomy including right lobectomy	
Malnutrition	Prolonged surgery with denervation of liver	
Renal insufficiency	<25 % of liver mass remaining	
Hyperbilirubinaemia	Surgical experience	
Thrombocytopenia	Ischaemia–reperfusion injury	
Lung disease	Hepatic parenchymal congestion	
Cirrhosis		
Age >65 years		

Most patients being planned for liver resections have colorectal liver metastasis and receive chemotherapy with 5-fluorouracil, oxaliplatin and irinotecan, and newer monoclonal antibodies cituximab and bevacizumab [7]. Chemotherapy induces marked histopathological changes in the liver parenchyma including fatty liver, chemotherapy-associated steatohepatitis (CASH), or sinusoidal injury (sinusoidal obstruction syndrome, SOS). CASH is pathognomonic of patients treated with irinotecan and is characterized by ‘steatosis, lobular inflammation and ballooning of hepatocytes’: also called the ‘grey liver syndrome’. SOS is caused by the use of oxaliplatin and the syndrome is called ‘blue liver syndrome’ because of the characteristic bluish-red hue of the firm liver [15, 16]. Irinotecan-induced CASH has been shown to be an independent risk factor for postoperative mortality and PLF. Oxaliplatin induced SOS develops after more than 6 cycles and is a risk factor for increased hospital stay and postoperative complications [17, 18].

Hepatic steatosis is a major determinant of postoperative outcomes. Over 20 % of patients undergoing a major liver resection have some degree of steatosis, significant enough to alter postoperative recovery [19]. Patients with biopsy-proven hepatic steatosis have a higher incidence of PLF (14 %) than patients with healthy livers (4 %) [20] even though the steatosis was of moderate grade. Belghiti et al. [21], reported a series of 478 patients who underwent liver resections, of which 37 patients had steatosis. Steatosis was an independent risk factor for postoperative complications (8 % of patients with steatosis), while only 2 % of patients with a normal histology developed complications. The increasing incidence of CASH, NASH and SOS has sparked interest in the use of preoperative liver biopsy as an assessment of the liver function and structure. Screening of high-risk patients (obese, high body mass index or those on chemotherapy) has been proposed. If a moderate degree of steatosis is established, these patients could benefit from manipulation of the volume, or surgery could be deferred till the acute changes subside either by treating the underlying aetiology or withdrawing the inciting agent.

Hepatitis B and hepatitis C virus infection-associated HCC develops along with the presence of fibrosis in the liver parenchyma. There is no correlation with fibrosis and liver resection, but when cirrhosis is established by a biopsy, it remains an

independent predictor of poor outcomes in terms of overall and tumour-free recurrence. Shen et al. used markers of liver fibrosis preoperatively to predict PLF in patients with HCC undergoing liver resection [22]. They evaluated preoperative hepatitis B virus (HBV) DNA levels, serum prealbumin (PA), hyaluronic acid (HA) and laminin (LN) levels and correlated these with PLF. A prospective model was used with these four laboratory results and validated in 89 HCC patients with a sensitivity and specificity of 62 % and 91 %, respectively.

Malnutrition is commonly prevalent among cirrhotics and leads to increased morbidity and mortality [23]. Malnutrition causes ‘disordered mitochondrial function’ which alters the immune response and thus reduces the hepatocyte regenerative capacity when exposed to ischaemia [24]. It is thus essential to objectively evaluate the nutritional status of all patients with liver disease, and to intervene with supplements as indicated.

PLF and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection but the predictive value for mortality is significantly higher when both systems fail simultaneously. Renal dysfunction following liver surgery may occur because of liver failure and hepatorenal syndrome but also due to hypovolaemia and release of free radicals and pro-inflammatory mediators during surgery [25].

Advanced age is no longer a deterrent to hepatic resections, which is now increasingly performed in elderly people with an acceptable morbidity and mortality [26]. Advancing age reduces the capacity of the liver to regenerate. The American Society of Anaesthesiology (ASA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores have proved useful in anticipating complications following major liver surgery [27].

Assessment of the true functional status of the liver is fraught with complexities and routine blood tests have proved unreliable predictors of PLF. Notwithstanding this, all patients planned for major liver resections should have complete liver biochemistry, a complete blood count and a prothrombin time as baseline investigations [10].

Experience in liver surgery/high volume centres show an inverse relationship with outcomes. It has been suggested that patients needing liver resections be referred to centres that perform 10–17 liver resections per year [28]. Massive estimated blood loss (EBL) remains a key prognostic factor for a safe resection. EBL correlates with the extent of resection and the number of segments resected [29] and this correlates with the incidence of PLF. Massive EBL during a major liver resection should be anticipated in tumours abutting the inferior vena cava or major hepatic veins, or if there is injury to the middle hepatic vein during resection, and not by patient age, tumour size alone, or type of hepatectomy. Cirrhosis creates a hyperdynamic milieu with increased cardiac output and decreased systemic vascular resistance. The hepatic buffer response of the cirrhotic liver is altered: portal blood flow is reduced/shunted as a result of collaterals in portal hypertension, and arterial blood flow is impeded because of hepatic fibrosis and sinusoidal resistance. This altered flow renders the cirrhotic liver relatively anoxic and less tolerant to hypotension and hypoxia.

An intraoperative blood loss greater than 1000 ml increases the risk of PLF [30]. This effect may be caused by a massive fluid shift secondary to EBL causing global

inflammation because of bacterial endotoxins, peripheral vasodilation and pooling in third spaces. Coagulopathy following blood loss with the inability of the liver to catch up, seems to increase the potential for intra-abdominal collections and bacterial infections. Avoiding prolonged hypotension and hypothermia by using judicious and timely transfusion, rapid infusion devices and safe surgical techniques is the key to salvage these patients. In fact, even major blood loss may be tolerated, if adequate efforts have been made to maintain euthermia, perfusion, avoid metabolic acidosis and provide an adequate and timely buffer against the dangerous triad of acidosis, hypothermia and coagulopathy resulting from EBL [30]. Prolonged operating time also leads to a poorer outcome and is extended in patients with EBL, vascular reconstructions and difficult surgery due to adhesions and tumour extensions into unsafe areas.

The functioning liver remnant (FLR) in patients has become a topic of much debate especially with the popularity of living donor liver transplantation. In a liver with normal parenchyma <25 % FLR is associated with a poor outcome, compared to that of patients with ≥ 25 % FLR [31]. The risk of PLF is 3 times greater. The FLR and the method of calculating it are even more important in livers with steatosis and fibrosis as in these livers functional reserve is markedly reduced. Patients with histologically proven parenchymal changes of steatosis, fibrosis or cirrhosis, mandate a FLR of up to 40 % [32].

Postoperative management has an important bearing on outcome. The first 48 h after a major hepatic surgery are crucial for a successful outcome. Metabolic, functional and haemodynamic alterations after hepatic resection are unique to each patient and demand specific management protocols. A multidisciplinary team approach is required with goal-directed therapeutic options. It is mandatory to have invasive haemodynamic monitoring, mechanical ventilation, critical parameter monitoring, strict antisepsis measures, metabolic control and optimal nutritional support.

Some degree of coagulopathy is the expected norm after a major hepatic resection and can be assessed by markers such as PT/INR, platelet counts and partial thromboplastin time (PTT). Postoperative coagulopathy peaks 48–96 h postoperatively and can be best monitored by a thromboelastograph (TEG) [33]. The underlying coagulopathy leads to postoperative haemorrhage and blood collecting in the abdomen, leading to postoperative infection.

Postoperative antibiotic prophylaxis does not control infections [34] and no effort should be spared in obtaining meticulous haemostasis and following strict infection control protocols.

3.4 Preoperative Risk Assessment

Preoperative risk assessment involves a thorough evaluation of all the factors mentioned above. A physical examination followed by appropriate clinical tests will identify patients at risk of developing PLF. The patient's liver status, hepatic reserve potential and functional aspect need to be investigated along with the metabolic and haematological derangements, which may lead to PLF.

Pre-existing liver disease can be determined by a thorough clinical history, recording previous blood transfusions, hidden illicit drug use, excessive ethanol use, history of jaundice, family history of familial cholestasis as well as history of adverse drug reactions. In India, it is important to take a history of use of complementary and alternative medicines (CAM) as many of them maybe hepatotoxic [35]. Physical examination should be able to pick up subtle signs of incipient liver failure and decompensation such as proximal muscle wasting, spider naevi, ascites and other signs.

Though routine liver tests have a low yield, they are of value in liver resections as the major indications for hepatectomy in eastern countries are HCC and in the West metastatic disease arising in either normal or cirrhotic livers. HCCs are usually sequelae of HBV/HCV disease and it is prudent to evaluate for active disease as well as cirrhosis. Though colorectal metastasis can occur in a liver with normal parenchyma, the widespread use of preoperative chemotherapy, as mentioned earlier, mandates a more thorough evaluation of steatohepatitis and fibrosis. In patients with HCC, cirrhosis is present in 64–74 %, but conversely in patients with cirrhosis there is only an 11 % incidence of HCC [36]. The rest would be divided equally between alcohol-related disease and HBV/HCV, with about 5 % due to metabolic factors. In a cirrhotic patient with HCC, it is the underlying liver parenchymal disease which precludes a safe liver resection and this needs to be addressed. A cirrhotic liver is much less rarely involved with metastasis in comparison to normal livers.

Liver tests may be labelled as

1. Screening tests to indicate the presence of liver disease
2. Diagnostic tests to discern aetiology
3. Quantitative tests to measure functional reserve.

3.4.1 Screening Tests

1. Serum bilirubin evaluates conjugation and excretion functions. Total bilirubin is a poorly sensitive and specific test for liver disease. Direct bilirubin does not differentiate between extra- and intrahepatic cholestasis. However, it is an important factor of scores such as CTP and MELD for prognostication. Miyagawa et al. [37] found no significant differences in morbidity and mortality after major hepatectomies in spite of a raised SB. Postoperatively, SB is often increased; however this does not always indicate impending PLF.
2. Serum bile acids evaluate excretion and shunting. Elevated bile acids are a good marker for portosystemic shunting with a sensitivity of over 90 % in detecting cirrhosis in patients with normal transaminases [38].
3. Alkaline phosphatase (ALP) evaluates cholestasis. It is also synthesized in the bone and placenta and is elevated in metastasis and thus is not a specific hepatic marker. ALP also has a lag curve in acute obstruction. High preoperative alkaline phosphatase level is indicative of metastatic disease and may be associated with increased

mortality after major resections [39]. Concomitant with a raised carcinoembryonic antigen (CEA) level, it should raise a strong suspicion of liver metastasis.

4. Gamma glutamyl transpeptidase (GGT) evaluates cholestasis, enzyme induction, alcohol abuse, renal failure, myocardial infarction, diabetes and pancreatic diseases, and intake of enzyme inducing agents. Elevation of both GGT and ALP indicates a hepatic origin for ALP elevation.
5. Transaminases evaluate necrosis and parenchymal damage. Raised serum levels do not correlate with the extent of parenchymal necrosis and have no prognostic value. Both enzymes are evaluated together as ALT is more liver specific and AST more sensitive to changes. After full course chemotherapy, transaminases can be elevated up to 2.5 times of normal. Partial hepatectomy induces only a mild-to-moderate increase in serum enzymes [40].
6. Coagulation factors and PT evaluate synthetic functions. PT is a routine investigation and is used in prognostic scores. As its half-life is shorter, it is a better index of the synthetic function than serum albumin, which has a half-life of 20 days. Fibrinogen levels in mild liver disease are normal/slightly elevated but markedly decreased in massive hepatocellular damage. If the prothrombin time is prolonged, a detailed evaluation of the coagulation system is warranted. Massive hepatectomy invariably leads to a fall in platelet counts and a depression of coagulation factors such as factors I, II, V, VII, X and plasminogen [40] with resultant disseminated intravascular coagulation (DIC).
7. Albumin evaluates synthesis. It is not only a part of the CTP score but is associated with many non-hepatic diseases such as renal disease, and nutritional entities such as protein malnutrition, protein-losing enteropathy and burns. Patients with preoperative albumin <3.0 g/dl are at risk of increased operative morbidity [41].

The serum concentrations of the above tests may not be truly reflective of liver function alone as many extrahepatic causes may also alter the results, e.g. transfusion associated haemolysis, resorption of haematomas, extrahepatic loss of albumin in bowel-related diseases, or altered PT due to a lack of absorption of vitamin K in either resected small bowel or due to absence of bile in the gut, i.e. obstructive jaundice. Moreover the production, excretion and absorption of these factors are varied and laboratory techniques also result in variances.

3.4.2 Diagnostic Tests

1. Acute hepatitis A: Hepatitis A IgM
2. Hepatitis B: Hepatitis B surface antigen, anti-HBs, anti-HBc, HBV DNA
3. Hepatitis C: Anti-HCV, HCV RNA
4. Primary biliary cirrhosis: Antimitochondrial antibodies
5. Primary sclerosing cholangitis: Antineutrophil antibodies
6. Haemochromatosis: Iron, iron-binding capacity, ferritin

Quantitative analysis of viral markers gives an idea of replicating viral activity and response to antiviral therapy.

3.4.3 Quantitative Tests

1. Aminopyrine breath test (ABT) evaluates microsomal function. Cytochrome P450-mediated N-demethylation of a ^{14}C - or ^{13}C -labelled methyl group of aminopyrine is measured. The formed $^{14}\text{CO}_2$ or $^{13}\text{CO}_2$ are trapped and measured. Merkel et al. [42] studied ABT and CTP scores and reported that both reliably predict death from liver failure in patients with cirrhosis. ABT had 94 % sensitivity and 88 % specificity and this was independent of the Child's classification. Though the test is easy to do, it has not become popular due to the need for expensive equipment.
2. Organic anionic dyes assess hepatic perfusion and excretory function. Normal liver cells take up sulphobromophthalein (BSP), conjugate it with glutathione and excrete into the bile. BSP clearance differentiates cirrhotic from non-cirrhotic livers and provides the status of hepatic uptake and biliary excretion. However, BSP is metabolized in the liver and has been reported to cause anaphylaxis, which has restricted its use. In contrast ICG is not metabolized in the liver.

The 15-min retention rate for indocyanine green (ICG15) is the most common preoperative test for evaluating hepatic reserve [43]. When a hepatectomy is done in a patient with a high ICG15 retention, the volume of non-tumorous liver resected must be minimized. Hepatic function is estimated by ICG15 or of its maximal removal rate (ICG-Rmax). The ICG15 should be approximately 10 % in normal persons. The threshold value for a safe major hepatectomy is set at 14 %, although the cut-off of ICG clearance has shown significant reduction in cirrhotic patients who underwent resection and died subsequently. This was most accurate on day 3 following surgery. When ICGR15 exceeds 20 %, a major hepatectomy should be deferred [43]. Patients with ICGR15 between 14 and 20 % benefit from volume manipulation to achieve a viable FLR.

Preoperative ICG clearance may predict 30-day hospital mortality in patients with cirrhosis [44]. With an accuracy of 100 % for prediction of long-term prognosis in both retrospectively and prospectively evaluated cases, Noguchi et al. [45] reported a ratio of ICG-Rmax relative to the FLR after hepatectomy, which could reliably predict outcome. Mainly researched by Japanese surgeons, ICG clearance has not been popular with other centres. An ICGR15 value of 14 % has been proposed as a cut-off for identifying patients who will have high postoperative morbidity following a major hepatic resection [45].

Recently, ICG has been investigated again. Fung et al. [46] studied liver stiffness (fibrosis) using a fibrosis measuring impedance elastograph. Although ICG extraction is unique to the liver with minimal extrahepatic elimination, the clearance rate is dependent on local and systemic haemodynamics. Any change in hepatic flow or systemic perfusion causes variances in ICG rates. Therefore, they correlated liver stiffness with ICGR15 and liver biochemistry, to determine its reliability in predicting postoperative outcomes. Liver stiffness correlated well with ICGR15 in liver resection patients, and predicted early postoperative complications and was recommended, to provide 'better prognostic information for patients undergoing resection.'

3. MEGX test: evaluates microsomal function and is a measure of the formation of the metabolite monoethylglycinexylidide (MEGX) after injection of a bolus of lidocaine and is evidence of the conversion rate of lidocaine by hepatic cytochrome P450. A value ≤ 25 $\mu\text{g/L}$ is related to PLF in patients with cirrhosis [47].
4. Technetium-99m galactosyl human serum albumin (99m Tc-GSA): GSA scintigraphy studies [48] have been reported to be useful for predicting the functional reserve of the liver and superior to ICG. 99m Tc-GSA is a scintigraphy agent that binds specific hepatic receptors, and can be used to assess the functional hepatocyte mass and thus the hepatic functional reserve in various physiological and pathological states. Unlike ICG it is not affected by the haemodynamic status.

3.5 Scoring Systems

Various scoring systems are in vogue to assess the suitability and risk stratification of hepatic resections in patients with cirrhosis. The CTP and MELD score were initially designed for other prognostications, and their validity in predicting PLF has been the objective of many trials. The results are inconsistent [1, 2, 5, 49]. In general, it is well accepted that a CTP class C patient is not suitable for any liver resection and those in class B are suitable for only minor liver resections [49].

Schroeder et al. [50] reported the superiority of CTP over the MELD score in predicting 30-day morbidity and mortality after hepatic resections. However, other studies validate the MELD score as a reliable predictor. A MELD score above 11 in patients with cirrhosis could predict PLF accurately [51].

3.6 Imaging

3D CT reconstructions or magnetic resonance imaging (MRI) reconstructions are now used exclusively for volumetric analysis and predicting FLR [52]. Calculation of FLR however remains a cause of disagreement and various techniques and calculations are in vogue. 3D reconstructions allow delineation of the hepatic veins, congestion volumes, exact tumour localization and facilitates virtual resection planning. However, imaging at present over estimates the FLR, and different formulae are in use, in an attempt to account for this error. The crux of any imaging or formula used is to ensure that the FLR is compatible with a smooth recovery and it is vital to assess the functional status of the FLR. Addition of preoperative hepatobiliary scintigraphy and CT volumetric measurement were performed by Dinant et al. in preoperative patients [48] to assess the accuracy of risk assessment for postoperative morbidity, liver failure and mortality. They concluded that using hepatobiliary scintigraphy with preoperative measurement of 99mTc-mebrofenin uptake in the FLR, proved more valuable than measurement of the FLR on CT alone in assessing the risk of PLF.

3.7 Prevention

Keeping the pathophysiology in mind, PLF can be prevented by a two-pronged strategy: Protect the parenchyma against damage and increase the parenchymal volume.

3.7.1 *Hepatoprotective Strategies*

1. **Ischaemic preconditioning:** After a brief period of inflow clamping, reperfusion is allowed, prior to the prolonged inflow clamping ischaemic insult (10 min of ischaemia and 10 min of reperfusion). It increases tolerance to the subsequent prolonged ischaemia and adenosine 5-triphosphate (ATP) depletion by exposing the parenchyma to brief intervals of anoxia and reperfusion before the final resection. It acts by presumably controlling IRI and retards the complement cascade. This reduces reperfusion injury particularly in steatotic patients. Clavien et al. [53, 54] did the initial trials and demonstrated a two-fold reduction in the postoperative serum transaminase levels. A reduced mass of apoptotic cells was noted on histopathology. A randomized trial by Chouker et al. [55] comparing ischaemic preconditioning and continuous clamping, showed stable cardiovascular haemodynamics, lowering the need for adrenaline/noradrenaline after liver reperfusion. Additionally, a recent Cochrane analysis observed no statistically significant difference in the mortality, liver failure, blood loss or haemodynamic changes [56]. However, length of hospital stay was significantly lower in the ischaemic preconditioning group.
2. **Intermittent vascular clamping:** consists of repeated periods of 15 min of inflow clamping followed by 5-min reperfusion phases. Belghiti et al. [57] reported that in contrast to the presumption, blood loss was significantly more in the intermittent clamping group. Acute phase liver enzymes and transaminase levels were significantly higher in the continuous portal triad clamping group than in the intermittent portal inflow clamping group when livers with chronic liver disease were included. Postoperative SB levels in cirrhotics were also significantly higher in the continuous inflow clamping group compared to the intermittent portal inflow cohort. They concluded that livers with chronic disease do not tolerate continuous vascular clamping as well as normal livers.
3. **Avoiding inflow clamping:** The Cochrane meta-analysis published in 2009 [56], based on three randomized trials, revealed statistically insignificant decreased blood loss with vascular clamping, when compared with no clamping. Total vascular occlusion is to be avoided unless resection is required at the cavohepatic junction when it cannot be avoided.
4. **Hypothermic liver preservation:** Interest in decreasing warm ischaemia of transported livers has spawned experiments into isolating the inflow and perfusing cold preservative into the future liver remnant, which is immersed in crushed ice to maintain the core temperature of the liver at 4 °C. Hypothermic liver preservation

when combined with total vascular exclusion attenuates IRI. In situ cold isolation techniques are still in their infancy and remain isolated case reports used in special situations with total vascular exclusion/cardiopulmonary bypass [58].

5. Pharmacological preconditioning: It has been reported in a clinical study that the use of isoflurane before clamping the inflow protected the liver from IRI [59]. Preconditioning with sevoflurane also significantly reduced postoperative transaminase levels and the overall incidence of postoperative complications was reduced especially in patients with fatty livers. Inhaled nitric oxide has also been cited to ‘significantly decreasing the length of hospital stay, improving serum transaminase levels and coagulation times, and reducing the number of apoptotic hepatocytes.’ A similar effect has been demonstrated with preoperative administration of 500 mg of methylprednisolone [59]. During major resections, intraoperative preconditioning with 600 mg of alpha-lipoic acid also reduced markers of hepatic damage by inflow occlusion.

3.7.2 Recommendations

Lesurtel et al. [60] have made the following recommendations: with better understanding of intrahepatic anatomy, newer energy devices and maintenance of a low central venous pressure during parenchymal transection, vascular clamping cannot be systematically recommended (level A). Portal inflow clamping reduces blood loss and use of blood products but does not influence morbidity (level A). Among various methods of inflow exclusion, they support intermittent clamping as better tolerated especially in patients with chronic liver disease (level A). Ischaemic preconditioning has been recommended for steatotic patients (level A). Intermittent clamping is preferred over ischaemic preconditioning in major liver resections and prolonged surgery (level A). Currently no evidence supports or refutes the use of ischaemic preconditioning in donor liver retrievals during living donor transplants.

3.7.3 Parenchymal Volume Management

Portal vein ligation (PVL/PVE) by ligation/embolization: PVL is usually performed by surgical ligation or percutaneously by transhepatic portal vein embolization (PVE). PVE induces apoptosis in the ipsilateral lobe, and hypertrophy and hyperplasia of the contralateral lobe. This increases the functional volume of the FLR, thus obviating hyperperfusion in a SFSS scenario. It is also a precursor phenomenon and predicts the regenerative response in the future remnant. PVE can increase contralateral lobe mass by up to 20 %, with the peak in growth occurring within 2–4 weeks of the procedure [61, 62]. The failure of the liver to enlarge after PVE is indicative of patients with impaired regenerative capacity in whom major resection should be avoided [62]. To prevent a surge in tumour growth due to enhanced differential hepatic artery flow to the tumour, local control by ablation/chemotherapy are also added as well as biliary drainage.

3.7.4 Splenic/Portal Inflow Modulation

Hyperperfusion of a small for size graft is often modulated by splenic inflow control by ligation/embolization or shunting. PLF is determined by haemodynamic parameters of the hepatic circulation and, specifically, by a portal blood flow that, when excessive for the volume of the liver parenchyma leads to an inflow/outflow mismatch causing pressure build up in sinusoids with a leaking capillary bed in the liver. Perisinusoidal and periportal haemorrhage occurs within a few minutes in a major hepatic resection as well as after the reperfusion of a SFSS graft. Late effects occur due to hepatic arterial and biliary epithelial hypoxia [6].

3.7.5 Staged Resections

ALPPS—the ‘associating liver partition and portal vein ligation in staged hepatectomy’ (ALPPS) strategy is one of the surgical innovations used to manage FLR volumes [63]. The ALPPS approach is proposed to induce rapid hypertrophy of the FLR in patients with HCC and whose preoperative volume does not allow a safe resection. The procedure entails the combination of in situ splitting of the liver along the Cantlie’s line and ligating the portal vein on the side of the tumour. Subsequently the second stage hepatectomy is done. The median FLR volume increase was 18.7 % within 1 week after the first phase and 38.6 % after the second [64, 65]. Recently, a number of trials comparing ALLPS and post-PVE liver resections have been published [66–68]. ALPPS has shown higher hypertrophy rates compared to PVE/PVL (40–80 % within a week compared to 8–27 %). However, ALPPS has higher sepsis rates (16–64 % of patients) and mortality rates (12–23 %).

ALPPS facilitates an early removal of tumours whilst waiting for an adequate FLR. Due to the high morbidity rates there has to be a strict criteria for selecting a patient for ALPPS as PVE has shown comparable FLR hypertrophy rates.

3.7.6 Different Tumour Strategies

Downsizing tumours with chemotherapy, local ablative techniques and embolization is yet another strategy to gain functional reserve volume when planning resections in livers, which are likely to have a low FLR.

3.8 Management of PLF

The typical clinical features of PLF parallel the clinical picture of ALF: coagulopathy, raised SB and encephalopathy. In addition renal failure, respiratory compromise, hypotension and features of sepsis may be present. This clinical presentation

parallels the presentation of ALF, but is closer to that of subacute liver failure than to that of hyperacute liver failure [69]. With deteriorating liver function the patient will develop hyperbilirubinaemia and coagulopathy which in particular is a poor prognostic marker [70].

If PLF is detected in a patient, it should be scored by the ISGLS system [2].

PLF grade A: should be monitored well, but may not require specific treatment.

PLF grade B: it has to be evaluated if the patient should be placed in an intensive care unit (ICU)

PLF grade C: need ICU care

Rahman et al. [71] have cited a daily measurement of serum C-reactive protein (CRP) as an early warning indicator of patients likely to develop PLF. Patients prone to developing PLF had a lower CRP level on POD 1 than patients who did not develop PLF. A prognostic utility of postoperative CRP was a serum CRP <32 g/dl, which was an independent predictor of PLF. Initial treatment of PLF is supportive: ventilatory support, vasopressors, renal replacement therapy and anti-sepsis protocols. Controlling coagulopathy and supporting nutrition are the other mainstays.

Patients of liver resections are normally monitored closely in the intensive care or high dependency units. It is normal for SB levels and the INR to rise in the first 2–3 days postoperatively. SB concentration above 50 $\mu\text{mol/l}$ (3 mg/dl) or INR greater than 1.7 on or beyond 5 days suggests liver dysfunction. Sepsis is indicated by raised serum lactate. The use of antibiotics in patients suffering from ALF is associated with a significant decrease in sepsis and this may also be of benefit in patients suffering from PLF [72]. Overall the management of PLF is along the lines for ALF. Identifying and controlling sepsis is the key to managing PLF [73].

Trials have shown that prophylactic antibiotics after liver resection do not lead to a reduction in PLF or sepsis [74]. ALF management guidelines propose that broad-spectrum antibiotics should be administered empirically to patients who progress to grade 3 or 4 hepatic encephalopathy, renal failure and/or worsening systemic inflammatory response syndrome (SIRS) [73, 75].

Many clinicians strive to provide hepatoprotection with N-acetylcysteine (NAC) [76]. However, no evidence exists that it has any benefit in ALF. NAC is advocated in the management of paracetamol-induced ALF and its use in non-paracetamol hepatic failure remains controversial. Sporadic papers do mention a benefit for NAC and it is used empirically for its anti-oxidant role. Early stage non-acetaminophen patients with ALF benefit from intravenous NAC. Patients with encephalopathy grades 3 or 4 do not benefit from NAC and will require emergency liver transplantation. NAC is commenced in a loading dose of 150 mg per kg per hour for 1 h followed by 12.5 mg per kg per hour for 4 h and 6.25 mg per kg per hour for the remaining 67 h.

The rest of the management is along supportive care protocols as shown in Table 3.2.

Hepatocyte transplantation has been used in trials as an effort to rejuvenate existing liver function. Intrahepatic hepatocyte infusion [77] has been used successfully to treat patients with certain metabolic disorders of the liver. Results in liver failure (ALF and PLF) have been poor due to insufficient delivery of viable and sustainable functional hepatocytes.

Table 3.2 Supportive care protocols

Support	Investigation	Intervention
Nutrition	Check serum albumin	Enteral preferred over parenteral Euglycaemia to be maintained
Respiratory	Acid–base gas analysis Chest X-ray Sputum culture	Control acid–base imbalance Chest physiotherapy Pulmonary toilet Early recognition of ARDS, ventilator support and weaning Avoid fluid overload
Renal	Urea, creatinine, electrolytes	Modify nephrotoxic drug dose/ avoid volume overload/ electrolyte imbalance Renal replacement therapy
Coagulopathy	INR, platelets, factors, TEG	Vitamin K and fresh frozen plasma if INR >1.5 or manifest bleeding Correct profound thrombocytopenia Recombinant factor VIIa (rFVIIa)(uncertain role)
Sepsis	Wound, ascites, drain, urine, sputum cultures CT abdomen for collections	Antibiotics to be started if encephalopathy worsens, worsening renal failure or SIRS parameters
Encephalopathy	CT head if worsening ICP monitoring	Lactulose
<i>Others</i> Stress ulcer prophylaxis Ascites Vascular events	Ultrasound Doppler	Proton pump inhibitors Large volume paracentesis Interventions

ARDS acute respiratory distress syndrome, *INR* international normalized ratio, *TEG* thromboelastograph, *SIRS* systemic inflammatory response syndrome, *ICP* intracranial pressure

Though, liver support systems have been available for some years now, their high operational cost and sepsis rates have not improved. These include:

1. Molecular absorbent recirculating system (MARS)
2. Modified fractionated plasma separation and adsorption (Prometheus)
3. Bioartificial liver (BAL) and extracorporeal liver assist device (ELAD).

Extracorporeal systems are predominantly sustained on albumin dialysis, and bioartificial devices are bioreactors with permeable membranes containing hepatocytes, either synthetic or natural. Very few trials exist in the setting of PLF, with the exception of one case series which showed no significant benefit [78, 79]. They are not currently recommended in the medical management of ALF. Because their actual place in the global field of acute or acute on chronic liver failure remains to be determined, their role in PLF is undefined. However, because outcomes in PLF are morbid, it is worthwhile to continue to investigate the beneficial roles of these devices [80–82].

3.9 Surgery

The use of a rescue hepatectomy (removal of necrotic portions or segments) in patients suffering from PLF may be of value when faced with a very sick patient. It is based on the concept that the 'necrotic liver' is the source of unknown humoral substances that contribute to SIRS [83].

The efficacy of orthotopic liver transplantation (OLT) for PLF has recently been reported [84]. In this paper, Otsuka et al. did a retrospective review of 435 patients who had a liver resection between 1990 and 2004. Nine of them (2 %) developed PLF of which seven were offered OLT at a mean of 25 days post resection. Indications for resection included malignancies and benign disease. Patients developing PLF had significantly altered biochemical and coagulation parameters manifesting on POD 2 and had the classical triad of coagulopathy, hyperbilirubinaemia and encephalopathy. There was no mortality following OLT, though one patient required a retransplant. The mean survival with and without OLT was 42.2 and 1.4 months, respectively ($p = 0.03$).

They concluded that all patients ($n = 4$) who suffered from PLF but were not considered suitable for liver transplantation, died, while all those undergoing OLT survived ($n = 7$). OLT allows salvage of an otherwise fatal condition. However, no definitive criteria are available for emergency liver transplantation for PLF.

OLT as a rescue for PLF has been gaining in popularity, governed only by the availability of organs or suitable donors in an emergency. The principles of transplantation should however be adhered to: in most instances the indications for OLT after PLF should be limited to patients who fulfill the primary indication for HCC—pre-resection tumour burden within the Milan criteria [85]. Patients with metastatic disease, beyond Milan criteria, advanced medical and anaesthetic comorbid conditions, and poor functional status, should not be candidates for OLT.

OLT is the only radical surgical remedy that improves survival in patients with end-stage liver disease. However, patients suffering from PLF are rarely eligible for liver transplantation because of tumour characteristics or comorbid conditions.

3.10 Conclusion

The incidence of PLF after a major hepatic resection averages 8 %. An abnormal FLR is the main cause for the pathogenesis of PLF. Other reasons, which worsen PLF, are hepatic parenchymal congestion, IRI and postoperative sepsis. These can exist singly or in combination.

Risk factors for the development of PLF are small FLR, blood loss, malnutrition, diabetes mellitus and active liver disease. A comprehensive preoperative assessment includes evaluation of liver volume, anatomy and function. A physical examination followed by appropriate clinical tests will identify patients at risk of developing PLF. The patient's liver status, hepatic reserve potential and functional aspect need to be investigated along with the metabolic and haematological derangements, which may lead to postoperative liver failure. Corrective measures should be applied when-

ever possible, as curative treatment options are limited. The risk of PLF is high when FLR is below 25–30 % in livers without cirrhosis and below 40 % in livers with pre-existing liver disease. PVE and/or two-stage hepatectomy are options when surgery cannot be deferred. Additional liver damage may be prevented by intermittent clamping techniques, though used with caution in steatotic livers. Management principles are on the lines of management of ALF with support of liver, cardiorespiratory and renal support function. Control of sepsis is an important aspect. Emergency liver transplantation has shown promise as a remedy for PLF.

Editorial Comments

Postoperative liver failure after hepatectomy is a potentially life-threatening complication. Fortunately, even though the rates of liver resection are increasing, the mortality from the procedure is decreasing. The operative mortality at specialized centres varies from 0 to 6 % [86]. However, the morbidity continues to be high. The definition of post-hepatectomy liver failure has not been standardized. Three definitions are currently being followed. Two of these (the 50–50 criteria and the International Study Group of Liver Surgery [ISGLS] criteria) have been mentioned by the authors [2, 5]. The latter not only diagnoses the condition, it stratifies the severity into 3 categories. Grade A does not need any change in management strategy, Grade B may be managed without any invasive intervention while Grade C needs alteration in management including invasive intervention. The ISGLS criteria have been validated by one study [87]. The study detected post-hepatectomy liver failure using this criteria in 11 % of patients—8 % had Grade A, 72 % Grade B and 20 % Grade C. The mortality in these patients was 0 % in grade A, 12 % in grade B and 54 % in grade C. Thus, the grading has been shown to correlate with mortality. However, in 2 separate reports, 41 and 67 % of patients fulfilling the ISGLS criteria recovered completely highlighting the importance of adequate management rather than just using the definition [4, 5].

The third definition described by Jarnagin et al. is simple. They define post-hepatectomy liver failure as high bilirubin in the absence of biliary obstruction or leak occurring with ascites and coagulopathy with or without encephalopathy [88].

The authors have discussed the possible pathophysiological factors in detail. To this I may add the possibility of hepatic venous outflow tract obstruction as described by Lhuire et al. [89] The authors documented outflow obstruction with contrast enhanced CT, Doppler ultrasound, cavography and assessment of pressure gradient between the hepatic vein and inferior vena cava. They managed the patient successfully with placement of a metallic stent in the left hepatic vein and documented reduction in the hepatic vein–inferior vena cava pressure gradient. The patient improved thereafter and was discharged. Hepatic venous outflow obstruction following hepatectomy has been reported in experimental studies in rats [90].

Various risk factors have been identified and have been discussed elaborately by the authors. This should allow surgeons to select proper patients for extensive resection to avoid post-hepatectomy liver failure. The main issue is the adequacy of the residual liver volume and presence of cirrhosis. While 30 % of residual volume is adequate for extended resections in a normal liver, it is grossly inadequate for a cirrhotic patient in whom at least 40 % of liver volume is required. This brings us to the question of increasing future liver remnant by various strategies. Both portal vein embolization (PVE) and liver partition with portal vein ligation are effective. However, the simplicity of PVE makes it the most used approach. It has the advantage of the tumour biology being assessed during the waiting period of 4–6 weeks. If the tumour progresses especially with chemotherapy the patient should not undergo liver resection. On the question of properly selecting patients for major resection in cirrhosis the prevailing guidelines should be followed. These are Child's A status, platelet count above 100,000/cm, absence of clinically significant portal hypertension, a future liver remnant of 40 %, and the 15 min indocyanine green (ICG) clearance of no more than 15 %. A number of tests are available to assess various functional aspects of the liver but they are cumbersome, not available at most centres and more importantly are not accurate with the exception of 15 min ICG clearance. Even this is not done routinely in the West.

Patients with features of postoperative liver failure by either the '50–50' criteria or the ISGLS criteria have circulatory changes as seen in septic shock such as vasodilatation, increased vascular permeability resulting in accumulation of fluid in the third space, tachycardia and increased cardiac output leading eventually to hypotension. Coagulopathy too is seen commonly. Altered kidney function usually occurs due to hepatorenal syndrome or acute tubular necrosis because of sustained hypotension causing compromised renal perfusion. With worsening renal function, fluid accumulates in the periphery or pulmonary bed. This often necessitates renal replacement therapy. With improvement in renal function the liver function also improves. Hepatic encephalopathy is seen more commonly in patients with renal failure because serum ammonia cannot be cleared by either the kidney or the liver. The presence of sepsis is another problem. Hypotension resulting from sepsis is detrimental to liver regeneration essentially due to ischaemia. Endotoxins produced in sepsis interfere with Kupffer cell activation and its function. One should not forget that following hepatic resection there is a depletion of Kupffer cells in the liver. Thus following hepatectomy there is a higher incidence of sepsis, and sepsis interferes with hepatic regeneration [91]. Therefore, every attempt must be made to avoid sepsis. Execution of the surgical procedure with utmost care avoiding excess blood loss, tissue necrosis, haematoma formation, prolonged ischaemia, etc. should minimize infection.

Management of post-hepatectomy liver failure has been duly addressed. I will emphasize on the fluid and nutrition therapy. Following hepatectomy the

urine output may be low but it is expected. It is not necessary to give bolus fluid therapy in these patients unless they are grossly oliguric. Cirrhotic patients should probably be given parenteral nutrition in place of dextrose solutions because parenteral preparations have branch chain amino acids, dextrose, medium chain triglycerides, phosphates and vitamins. Usually up to 2 l of such fluid is necessary. If volume deficit exists, it should be managed with additional fluids. Parenteral nutrition in post-hepatectomy liver failure helps liver regeneration and decreases septic complications. The addition of phosphate is extremely important because it is necessary for both energy production and liver regeneration. Moreover the phosphate level goes down considerably after major liver resection [92]. Since the available phosphate solutions contain potassium, these may need to be stopped if the serum potassium level is high. The phosphate will then need to be replaced orally and the oral forms have sodium. Hence, the serum sodium would need to be monitored.

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