REVIEW ARTICLE

Systematic review of pathophysiological changes following hepatic resection

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Abstract

Objectives: Major hepatic resection is now performed frequently and with relative safety, but is accompanied by significant pathophysiological changes. The aim of this review is to describe these changes along with interventions that may help reduce the risk for adverse outcomes after major hepatic resection.

Methods: The MEDLINE, EMBASE and CENTRAL databases were searched for relevant literature published from January 2000 to December 2011. Broad subject headings were 'hepatectomy/', 'liver function/', 'liver failure/' and 'physiology/'.

Results: Predictable changes in blood biochemistry and coagulation occur following major hepatic resection and alterations from the expected path indicate a complicated course. Susceptibility to sepsis, functional renal impairment, and altered energy metabolism are important sequelae of post-resection liver failure.

Conclusions: The pathophysiology of post-resection liver failure is difficult to reverse and thus strategies aimed at prevention are key to reducing morbidity and mortality after liver surgery.

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Introduction

Liver resection for primary and selected metastatic hepatic neoplasms can be performed safely with low rates of morbidity and mortality.[1] However, major liver resection is accompanied by significant and to some extent predicable pathophysiological changes. These range from mild transient abnormalities to progressive derangements that can be life-threatening in the case of post-resection liver failure (PLF).[2] Patients with pre-existent parenchymal liver disease and/or a small residual liver volume (RLV) are at greatest risk for PLF,[1,2] the clinical features of which are similar to those of liver failure in other contexts and include coagulopathy, encephalopathy, jaundice and ascites. A comprehensive understanding of the pathophysiological changes that can be expected after major hepatic resection is important to enable surgeons to recognize deviations from the normal course at an early stage. The aim of this review is to describe the pathophysiological changes that occur following major hepatic resection and interventions that may prevent or reduce the risk for the development of those complications specifically associated with hepatic resection.

Materials and methods

A literature search was performed using the MEDLINE, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) databases for articles published from January 2000 to December 2011. The medical subgroup headings (MeSH) 'hepatectomy/', 'liver function/', 'liver failure/' and 'physiology/' were used as broad search terms. The search was performed according to PRISMA (*p*referred *r*eporting *it*ems for *s*ystematic reviews and *m*eta-*a*nalyses) recommendations (Fig. 1). To outline key components of pathophysiological change after liver resection, the above MeSH terms were combined using Boolean operators with the MeSH terms 'reperfusion injury/', 'liver ischaemia/', 'immunity/', 'liver circulation/', 'blood coagulation/', 'blood cell count/', 'metabolism/', 'liver function tests/', 'kidney function/', 'liver regeneration/' and 'liver hypertrophy/'. Additional articles were identified from the references of articles highlighted by the electronic search. Eligibility criteria required studies to have been published from January 2000 onwards, to refer to investigations in humans in which more than eight patients underwent major hepatectomy, and allowed the inclusion of randomized and non-randomized studies including
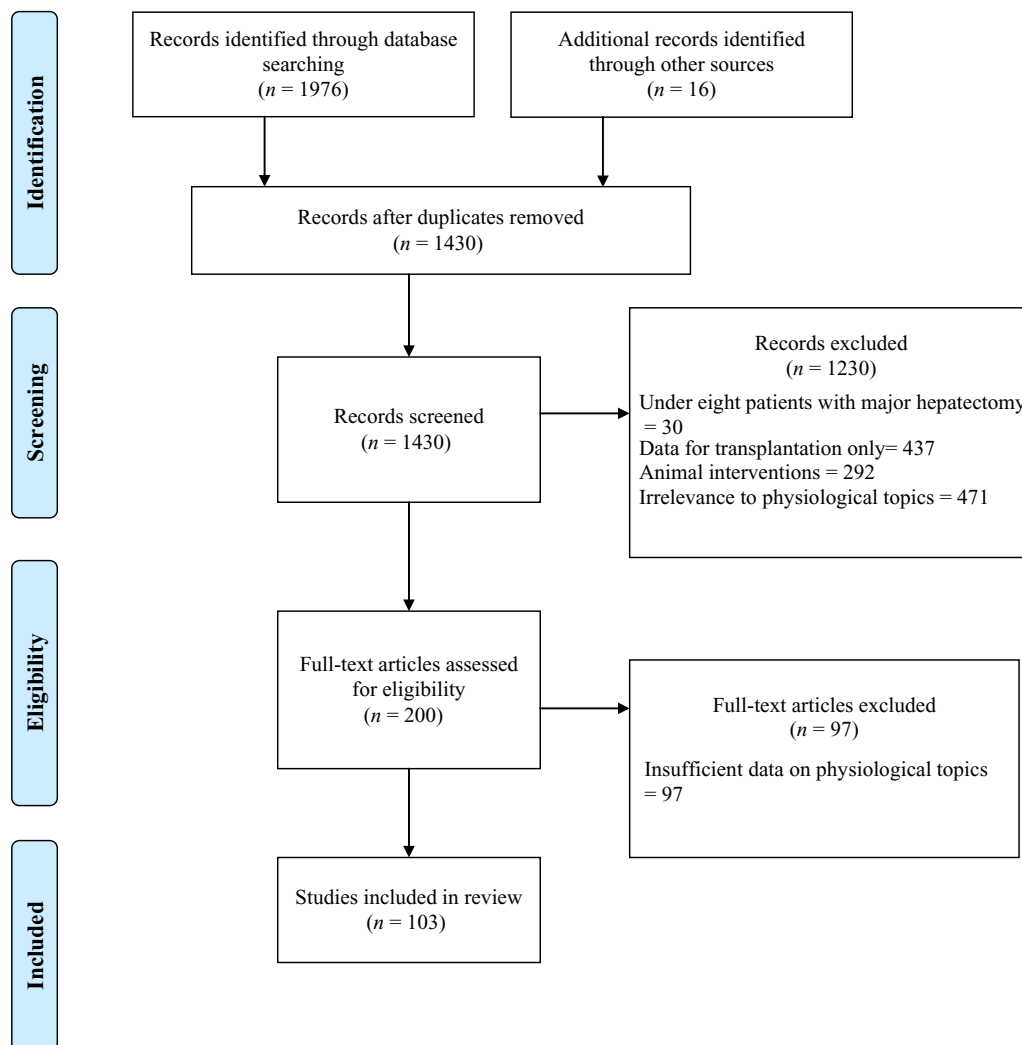
Figure 1 Flow diagram showing the identification and screening of studies for review in line with PRISMA criteria

observational studies without control groups, individual studies and reviews with relevance to physiological topics. Exclusion criteria discounted animal studies, studies in which only transplantation was performed, studies reported in languages other than English and studies with insufficient data on physiological topics. The selection of articles was conducted by two reviewers. Any data obtained were confirmed by at least one other reviewer.

Results

Biochemical liver function tests

Commonly measured biochemical parameters of hepatic function following liver resection include aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), bilirubin, albumin and C-reactive protein (CRP). Time-dependent change, influencing factors and aetiologies of change are shown in Table 1.

Serum levels of bilirubin are dependent on the pre-hepatic load of haem, hepatocellular function and rate of biliary excretion, all of which can be altered in the postoperative period. A landmark study by Balzan et al.,[3] carried out in 2005, found that serum bilirubin of >50 µmol/l combined with prothrombin time (PT) of <50% of normal time (the so-called '50–50' criteria) at day 5 was associated with an odds ratio (OR) of 216 [95% confidence interval (CI) 54–861] for predicting postoperative mortality with an accuracy of 97.7%. The presence of either of these criteria alone at any time after surgery was also associated with marked increases in postoperative mortality.[3]

Albumin and CRP are synthesized by the liver and their postoperative change has been studied in detail (Table 1). At day 1, median albumin levels were found to be reduced from 42 g/l [interquartile range (IQR): 38–46 g/l] and 44 g/l (IQR: 40–46 g/l) to 26 g/l (IQR: 22–31 g/l) and 24 g/l (IQR: 21–26 g/l) in patients submitted to minor and major hepatic resections, respectively.[4] At

Table 1 Changes to biochemical markers following hepatic resection

Test	Peak or trough	Influencing factors	Marker of:
Transaminases (AST/ALT)[1,4,92]	Peak at day 1 followed by exponential decay	Time of surgery and hepatic ischaemia Bilirubin level	Hepatocellular injury
Bilirubin[2–4,93]	Peak at day 3 (variable), biphasic Falls at 3–12 μmol/day Early postoperative period: Unconjugated/conjugated ratio: >1 Late postoperative period: Unconjugated/conjugated ratio: <1	Day 1: preoperative bilirubin, duration of surgery, blood transfused Days 1–7: volume hepatic resection, hepatic ischaemic time >Day 7: sepsis	Preload of haem Hepatocellular function Rate of biliary excretion Sepsis
C-reactive protein[4,94]	Peak at day 3	Rise is inversely proportional to extent of resection (days 1–5)	Synthetic function Hepatic failure following major hepatic resection (<32 mg/l at day 1) Complication (days 3–7)
Albumin[4,94]	Trough (>day 7) then slowly recovers	Proportional to extent of resection Presence of complication (days 1–5)	Synthetic function Complication (days 1–7)
ALP, GGT[93]	Trough to approximately 7% of initial value then slowly climbs at rate 14 U/l/day GGT greater variability	Presence of biliary obstruction (can be diagnosed by confirming elevated cholesterol level) Recovery correlates with normalization of prothrombin activity	Regeneration
α-GST[95]	Peaks at 15–30 min after reperfusion	Preconditioning can be protective	Ischaemia Postoperative hepatic dysfunction (>490 μg/l at 2 h post-resection)
Glucose[20,23,24,96]	Rises within minutes of reperfusion; elevation can persist for up to 16 h	Chronic liver disease or fibrosis Hormonal manipulation (insulin, cortisol, glucagon, noradrenaline) Portal clamping	Glycogenolysis Gluconeogenesis
Lactate[20–22,92,93,97]	Rises within minutes of reperfusion and returns to normal within 24 h Represents adequate capacity of remnant	Degree of ischaemia (correlates with AST rise) Pre-existing liver disease	Ischaemia–reperfusion injury Anaerobic hepatic metabolism Systemic levels of lactate but not intestinal lactate levels Level >4–5 mmol/l associated with hepatic failure (although time course may be more important)
Serum creatinine[45,46]	Little change in immediate postoperative period Patients with a preoperative serum creatinine of ≥ 155 mmol/l are less predictable Peaks at days 2–3	Raised preoperative serum creatinine Impaired neurohumoral autoregulation (diabetes, ischaemic heart disease, hypertension) Perioperative hypotension (low CVP) Late sepsis/multi-organ failure, post-resection liver failure	Acute kidney injury Haemofiltration requirement
Phosphate/Ca^{2+}[16–19]	Hypophosphataemia almost universal (mean drop 47%) Severe in up to 20% of patients Nadir seen on days 2–3 and recovers by day 7 Ca^{2+} reaches nadir 24 h earlier than PO$_{4-}$	Size of fall inversely proportional to hepatic remnant volume and rise in ALP Inversely proportional to prothrombin level	Increased urinary loss of phosphate: mechanism unclear

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; α-GST, α-glutathione S-transferase.

day 7, median values of albumin appeared to remain significantly lower than preoperative values at 32 g/l (IQR: 28–36 g/l) and 31 g/l (IQR: 28–33 g/l) in patients undergoing minor and major hepatic resections, respectively.[4] Acute changes in serum albumin reflect the movement of albumin into the interstitial space in response to tissue injury, rather than reduced liver synthesis, and are exaggerated by systemic complications such as sepsis. The CRP peaked at day 3 at 138 mg/l (IQR: 104–166 mg/l) and 86 mg/l (IQR: 60–125 mg/l) in patients submitted to minor and major hepatic resections, respectively.[4]

Levels of ALP and GGT rise during the first week after major resection and remain elevated during the period of liver regeneration. The increases in ALP and GGT may be exaggerated in pathological situations such as biliary obstruction or small-for-size syndrome, in which intrahepatic cholestasis occurs.[5]

The administration of pre- and perioperative methyl prednisone to patients undergoing hepatic resection has been shown to reduce postoperative peaks in bilirubin and CRP levels, but no differences have been noted in transaminase levels or the occurrence of complications.[6]

Coagulation changes after hepatic resection

The homeostasis of the coagulation system is closely related to hepatic function because the liver is responsible for the synthesis of factors involved in the coagulation and fibrinolytic pathways, as well as regulation of their activators and inhibitors. The liver is also, via the reticuloendothelial system, largely responsible for the clearance of breakdown products of activated clotting factors.[7] Thus, in patients with underlying cirrhosis, preoperative abnormalities in the clotting and fibrinolytic systems may coexist.[7] The platelet count is also reduced in portal hypertension. Patients with prolonged obstructive jaundice may develop vitamin K deficiency that results in alterations in both the clotting system via factors II, VII, IX and X and the anticoagulant system via proteins C and S.[7] The magnitude of the changes to the coagulation profile have been correlated with the extent of hepatic resection (weight of resected specimen),[8,9] amount of blood loss[8] and time of surgery.[9] In addition, the degree of change in the level of any individual factor will be governed not only by impaired synthesis, but also by the rate of consumption and half-life dependent decay.

Activated partial thromboplastin time (aPPT) and PT, or the international normalized ratio (INR), are the most commonly measured parameters of coagulation following hepatic surgery (Table 2). In assessing the frequency at which these changes

(aPPT, INR) occur, it is important to take into consideration the proportion of patients undergoing major hepatic resection,[10,11] the extent of blood loss[11] and the amount of i.v. fluid administered[11] in association with the resection. In a series of 124 patients with normal underlying hepatic function, in whom the mean ± standard deviation (SD) weight of the hepatic resection was 667 ± 443 g, PT was prolonged in 43% of patients at day 3 and in 22% at day 7,[9] with a mean ± SD maximal value of 18 ± 3.8 s (normal range: 11–16 s). It is also worth noting that some of the immediate postoperative changes reflect the diluting effect of the administration of i.v. fluid, whereas those at 24 h and later reflect the amount of liver resected.[11]

Three studies[8,9,11] have looked at the effect on platelets following hepatic resection (Table 2). As expected, given that platelets are not synthesized in the liver, the level of reduction was correlated with the amount of blood loss and the amount of intraoperative fluid administered, but not with the amount of liver resected.[11]

Antithrombin III (AT-III) is a serine protease inhibitor that is synthesized in the liver.[10] It acts to neutralize thrombin and factor Xa.[10] Bezeaud *et al.* showed a fall to <50% of baseline, which persisted to day 5 and coincided with similarly sized reductions in levels of the coagulation inhibitor protein C.[12] The same study[12] measured levels of the prothrombotic marker thrombin-antithrombin. The level of plasma thrombin–antithrombin complexes indicate the degree of intravascular thrombin formation.[12] In this study,[12] despite the administration of prophylactic low molecular weight heparin, a 10-fold increase in plasma levels of thrombin–antithrombin complexes was observed from the immediate postoperative period through to day 5. This has particular clinical significance: firstly, higher levels of thrombin–antithrombin complexes within the first 48 h after surgery were associated with an increased risk for subsequent thrombotic complications, and, secondly, it questions what the most appropriate thrombotic prophylactic might be, given the acquired antithrombin deficiency.[12] Further evidence to support the development of a procoagulant state following partial hepatic resection has included the observation of increased factor VIII and von Willebrand factor between days 1 and 5.[12]

Fibrinogen is an acute phase protein synthesized within the liver. It is required for clot formation. Fibrinogen is expected to increase following surgical trauma.[13] After hepatic resection, this increase has been found to be dampened proportional to the magnitude of the hepatic resection.[13] In addition, a temporal failure to increase in the postoperative period is a predictor of complications.[13]

Thus, it is clear that the balance between an anticoagulated and thrombotic state is dependent on a complex interaction of multiple factors. Standard clotting profiles would not seem to offer an accurate or real-time assessment of the true underlying situation or predict the likelihood of bleeding or complications. As more detailed methods of making a real-time assessment of the clotting pathways become commercially available, it may be appropriate

Table 2 Summary of changes in coagulation system following hepatic resection

Factor	Test	Main findings
II, VII, IX, X[8–11]	INR/PT	Immediate rise, peaks at days 1–3, normalizes at day 5
I, II, V, VIII, IX–XII[8,10]	aPPT	Small immediate rise, peaks (40–50 s) within 24 h and normalizes within 48 h
Platelets[8,9,11]	Platelets	Non-clinically significant fall with nadir at day 3 returning to normal at day 5
Antithrombin III[10,12]	AT-3	Extent of nadir proportional to extent of hepatic resection Level of <60% of baseline is associated with procoagulant state
Protein C[12]	Protein C	Fall proportional to fall in AT-3
Protein S[12]	Protein S	Transient fall returning to normal within 24 h (extrahepatic synthesis)
Fibrinogen[13]	Fibrinogen	Dampened rise post-resection proportional to magnitude of resection

INR, international normalized ratio; PT, prothrombin time.

to use these to tailor therapies to combat individually identified deficiencies.

Clinical trials of thromboembolic prophylaxis specifically after liver resection are lacking. However, patients undergoing major abdominal surgery benefit from thromboembolic prophylaxis and available evidence suggests that this is safe and effective in patients undergoing liver resection,[14] which is consistent with the known effects of liver resection on both the pro- and anticoagulation pathways.

Metabolic changes

Energy consumption by the liver following hepatic resection increases to support protein synthesis for the acute phase response to injury.[15] However, hepatocyte mitosis during liver regeneration incurs an additional burden in the maintenance of metabolic function despite a decrease in liver mass.[1,15] As a result of competing metabolic demands, an economic energy crisis occurs, with a fall in energy state or 'energy charge', and some synthetic and excretory functions are sacrificed.[1] As energy production capacity increases with successful regeneration, liver function recovers.[15]

Serum calcium and phosphate levels drop significantly in the early postoperative period (Table 1).[16–19] The routine treatment of these remains controversial because although severe hypophosphataemia can cause life-threatening complications, it is not clear whether routine treatment reduces complications[16,18] in healthy patients. It would seem appropriate to institute phosphate replacement should levels fall to <0.7 mg/dl.

Glucose homeostasis is maintained to a significant extent by hepatic gluconeogenesis. The liver has a key role in the regulation of plasma concentrations of lactate, a precursor of glucose,[20] and maintains up to 50% of the decomposition of lactate primarily via gluconeogenesis.[20] The liver can change from a lactate consumer to a lactate producer by switching to anaerobic metabolism when there is a reduced oxygen supply, such as during vascular clamping in hepatic resection.[20–22] Hyperglycaemia (Table 1) induced by surgical stress is also recognized following liver resection.[23] This, in turn, impairs liver metabolism and immune function, thus impacting on postoperative recovery.[24]

The liver plays an important role in amino acid metabolism, protein synthesis and protein breakdown. It detoxifies end-products of the intestinal metabolism, such as ammonia. Hyperammonaemia is probably a causal component of hepatic encephalopathy.[25] An imbalance in plasma amino acids, which is closely associated with hyperammonaemia,[25] during liver failure has also been implicated, and can be measured by the ratio between branched-chain amino acids (BCAAs) and the aromatic amino acids (AAAs), otherwise known as Fischer's ratio.[26] Fischer's ratio is a useful indicator of the severity of hepatic parenchymal injury in patients with liver disease and severe hepatic insufficiency.[26] The pathophysiology of hyperammonaemia in liver disease is complex. In 2008, van de Poll *et al.* reported that the net splanchnic contribution of ammonia is only minor because ammonia acid supply and metabolism per gram of liver increase

significantly immediately following hepatectomy.[27] It has been shown that hepatocellular ammonia clearance is also likely to be preserved in the diseased liver.[27] Therefore, even the diseased liver has substantial reserve capacity. The kidneys also have a significant role in the regulation of systemic ammonia release and thus therapies aiming to reduce high ammonia levels may need to target renal ammonia production and excretion in addition to intestinal ammonia production.[27]

Amino acid imbalance with a reduced Fischer's ratio in the diseased or injured liver is caused by an increase in BCAA catabolism in muscle and decreased AAA breakdown in the liver.[25] A reduction in the insulin/glucagon ratio may play a role in this metabolic imbalance[25] and may be reversed by supplemental BCAA.[28] In addition, the administration of BCAAs after major hepatectomy has been shown to support protein synthesis and regeneration of the remnant liver.[26] Use of molecular adsorbent recirculating systems (MARS) during liver failure suggests that a low Fischer ratio can be corrected by recirculating albumin dialysis; however, experience with MARS for PLF is limited and there is no evidence to date that clinical outcome is altered.[25,29]

The effects of the Pringle manoeuvre on amino acid metabolism alter individual amino acid levels, but the Fischer ratio remains unchanged.[25] In 2007, Dejong *et al.* found that in patients who underwent hepatic resection without a Pringle manoeuvre the Fischer ratio remained unchanged, but plasma AAA levels were inversely correlated with RLV.[25]

Previous studies have shown a correlation of the ratio between BCAAs and tyrosine (BTR) with liver function parameters such as prothrombin and albumin in patients with liver disease.[26] Increased BTR levels after hepatectomy were found to be associated with the prolonging of jaundice after liver surgery.[26]

Immune function

Rates of postoperative infection may reach 50% after major liver resection[30] and bacterial infection may develop in up to 80% of patients with PLF in comparison with 20% of patients who do not have PLF.[30] Sepsis is the most common immediate cause of death in patients with PLF. Several factors contribute to increased susceptibility to infection and the development of sepsis in patients following liver resection. These include technical factors such as wounds and collections of bile or blood, reduced capacity of the reticuloendothelial system,[31] and increased exposure to enteric microorganisms, all of which occur in the setting of a surgical stress response.[32]

Sepsis can also precipitate or exacerbate PLF as a result of the inhibitory effect of sepsis on hepatic regeneration.[1] Systemic inflammatory response syndrome (SIRS) is likely to be implicated in sepsis and end-organ dysfunction in PLF.[32] This syndrome is an index of surgical stress early after surgery and is predictive of complications.[33] Patients with sepsis can develop circulatory dysfunction as a result of haemodynamic instability and decreased systemic vascular resistance.[2,34] This may be further complicated by the rapid development of multi-organ failure, such as in acute

renal failure and acute respiratory dysfunction.[2,34] The majority of PLF patients will develop SIRS and multi-organ failure, and an 80% mortality rate has been documented in patients who undergo resection of >50% of the liver.[30,35]

The reticuloendothelial system or Kupffer cell mass and function are reduced and show an S-shaped correlation to the extent of resection.[31] Kupffer cells play a significant role in the innate immune system and produce cytokines [tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6)], which induce proliferation of hepatocytes.[1] Thus the remnant liver is dependent on Kupffer cells for regeneration as well as for the clearance of blood-borne enteric microorganisms and endotoxins. Recovery of Kupffer cell function may not occur for >2 weeks after resection.[1]

The increased rate of bacterial translocation to the liver from portal and arterial blood, mesenteric lymph nodes and other organs may be attributed to reduced clearance and possibly to the application of temporary hepatic inflow occlusion.[1] Bacterial endotoxins directly affect Kupffer cells by impairing the initiator cytokines needed for regeneration.[1] They also disrupt hepatocyte transport mechanisms, membrane function and metabolism, leading to hepatic necrosis.[2]

The liver responds to injury and infection by producing an acute phase response in preparation for change in metabolic processes, the removal of necrotic tissue, the mobilization of immune cells and the reparative process.[32,35] An excessive inflammatory response with subsequent transient immunosuppression can lead to increased susceptibility to infection, SIRS and consequent multi-organ failure.[35] Portal venous congestion associated with hepatic inflow occlusion can upregulate the production of acute inflammatory cytokines.[36] A higher portal vein pressure correlates with an increased inflammatory response and repeated intermittent clamping has been proposed as a method to overcome this.[36]

Plasma IL-6, IL-10, IL-8, monocyte chemotactic protein-1 (MCP1), cortisol and leptin have been positively correlated with infection and organ dysfunction following hepatic resection.[32] Surgical stress causes an increase in energy requirements; however, there is a decrease in hepatic energy levels in the first 48 h after resection,[37] which impairs liver regeneration. The ongoing inflammatory activity in patients with chronic liver failure further increases the risk for acute liver failure[38] as a result of these patients' reduced ability to adapt to surgical stress.[39]

Several randomized controlled trials (RCTs) indicate that high-dose steroid administration attenuates the surgical stress response while reducing immune suppression in patients undergoing hepatectomy.[35,40,41] However, there is no evidence that this leads to an improvement in clinically important endpoints.[35,40,41]

Strey *et al.* confirmed the role of complement activation in the systemic inflammatory response whereby complement products return to baseline by day 7.[42] Early increases in C3a and soluble terminal complex sC5b9 were found to be accompanied by an early reduction in C4a and C5a.[42] The same study found a decrease in neutrophil chemotaxis and function, which suggests the downregulation of neutrophil activity following hepatic resection.

However, only a reduction in C5L2 on monocytes was associated with the impairment of postoperative liver function (bilirubin and thromboplastin time) and no other postoperative clinical data, such as incidence of complications, were given.[42]

Renal function

Two large series have shown postoperative acute kidney injury (AKI) occurs in 15% of patients undergoing hepatic resection (Table 1).[43,44] Postoperative AKI is strongly associated with mortality, which reaches 22.5% in patients with and 0.8% in those without AKI ($P < 0.001$), as well as extended requirements for intensive care unit (ICU) and hospital care.[43] The four strongest predictors[43] of postoperative AKI are preoperatively elevated ALT, pre-existing cardiovascular disease, chronic renal failure[45,46] and diabetes.[43] Such patients have an impaired ability to autoregulate glomerular blood flow during surgery and thus have an increased risk for acute tubular necrosis.[45]

Increased blood loss during hepatic resection has been associated with greater risk for AKI.[47] Low (<5 mmHg) intraoperative central venous pressure (CVP) and fluid restriction are applied in many centres to reduce blood loss.[43,44,48] However, the use of low CVP needs to be balanced against the risk for AKI.[43,48] If mean arterial blood pressure (MABP) falls to <80 mmHg, the glomerular filtration rate (GFR) drops significantly, leading to an increased risk for the development of AKI.[43,44] Postoperative renal function may be impaired by a low arterial blood pressure[43] arising from the hypovolaemic state caused by low CVP anaesthesia and portal inflow occlusion. A low perfusion state can also occur secondary to cardiac dysfunction or distributive circulatory changes, such as sepsis or hepatorenal failure.[45] Patients who develop PLF show haemodynamic changes similar to those in patients with cirrhosis or acute liver failure of other causes and are at risk for hepatorenal syndrome, particularly when bacterial sepsis ensues.[43,44] Cardiac output is increased and blood flow is redistributed towards the splanchnic circulation and away from the systemic vascular bed in response to increased levels of nitric oxide (NO).[43,44] These changes lead to reduced central and arterial blood volume, low pulmonary capillary wedge pressure, low CVP, low systemic vascular resistance, increased carbon monoxide, and reduced MABP.[43,44] Hepatorenal syndrome results from reduced renal blood flow and activation of homeostatic mechanisms that produce renal arteriolar vasoconstriction.[43,44] Perioperative management to prevent mortality from hepatorenal syndrome includes optimizing the patient's fluid status,[43] and remaining vigilant for and providing early management of sepsis.[30] Terlipressin is a vasopressin analogue that redistributes blood flow from the splanchnic to the renal circulation.[49] In the setting of chronic liver disease, terlipressin, alone or with albumin, reduces the mortality associated with hepatorenal syndrome.[49] The role of terlipressin in PLF has not been tested, but it is reasonable to consider that it may be beneficial in patients who develop hepatorenal failure in this context.

Table 3 Factors controlling and interventions affecting hepatic blood flow (HBF)

Level	Flow	Regulation	Effect of intervention
Systemic[50,98,99]	Total HBF	↓ in HBF seen with: • ↓ CO • ↓ SVR (other than splanchnic) • ↑ RAP > PVP	Inflow occlusion results in: • ↓ MAP and ↓ CVP • ↓ Blood loss Hepatic venous exclusion: • Well tolerated • ↓ CVP and CO • MAP maintained >55 mmHg as a result of ↑ in SVR Infrahepatic caval clamping: • Well tolerated • ↓ Blood loss
Regional[50,66,100,101]	Total HBF	Total HBF (constant) = HAF + PVF (hepatic arterial buffer response)	Inflow occlusion followed by reperfusion results in • ↓ SVR: • Total HBF constant When preconditioning used: • Total HBF Laparoscopic surgery: • No difference in effect of inflow occlusion using laparoscopic or open surgery
	PVF	Passively drains splanchnic arterial bed so ↓ splanchnic flow results in ↓ PVF	Inflow occlusion followed by reperfusion results in: • 29% ↓ in PVF on reperfusion lasting >30 min When preconditioning used: • No change in PVF
	HAF	No auto-regulatory activity ↓ HAF with ↑ arterial resistance Arterial resistance ↑ with ↑ PVF (hepatic arterial buffer response)	Inflow occlusion followed by reperfusion results in: • 8% ↑ in HAF on reperfusion lasting >30 min When preconditioning used: • 200% ↑ in HAF
Micro[50,66]	HSF	Flow controlled by diameter of the sinusoids Sinusoidal diameter controlled by sinusoidal endothelial cells, hepatic stellate cells and Kupffer cells Mediators released by above cells alter degree of contraction or relaxation of the cells, thus altering sinusoidal diameter and hence resistance to flow	Ischaemia and subsequent reperfusion create a mismatch in time and space of mediator release so that homeostasis of the mediators is lost

CO, cardiac output; CVP, central venous pressure; HAF, hepatic artery flow; HSF, hepatic sinusoidal flow; MAP, mean arterial pressure; PVF, portal blood flow; PVP, portal blood pressure; RAP, right atrial pressure; SVR, systemic vascular resistance.

Hepatic blood flow

Hepatic blood flow is complex and regulated at three levels in normal physiological situations: the systemic circulation; the regional (macro) circulation, and the micro circulation.[50] Factors controlling each of these levels and the effects of interventions are shown in Table 3.

Ischaemia and reperfusion

Ischaemia–reperfusion injury (IRI) occurs following liver resection with hepatic inflow occlusion. The severity of hepatic IRI correlates with the time of ischaemia and clinical factors, such as the duration of the procedure, periods of intraoperative hypotension and the degree of splanchnic ischaemia, most of which are under the surgeon's control.[51] In addition to ischaemic injury to the liver, hepatic portal triad clamping causes intestinal venous congestion.[36,51] Stagnant portal venous blood stimulates inflammatory mediators that exacerbate IRI to the liver.[36] The reflow of stagnant portal venous blood into the ischaemic liver is detrimental to hepatic energy metabolism and therefore subsequently affects the liver's ability to maintain function and regenerate.[51]
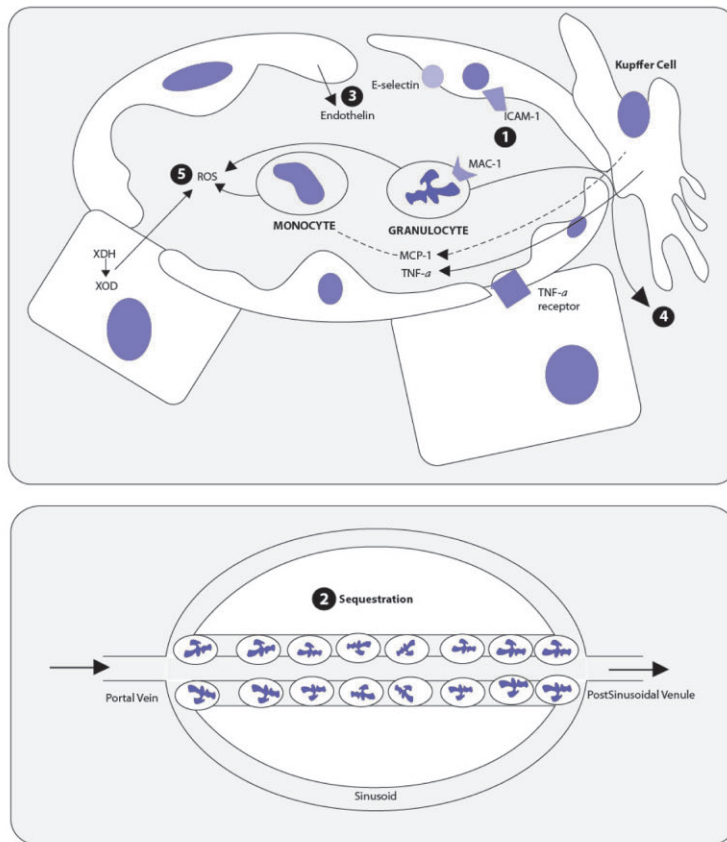
Diseased hepatic parenchyma is more susceptible to IRI[51–53] and should not be exposed to >60 min of continuous warm ischaemia,[40] although periods of up to 90 min have been shown to be well tolerated by normal liver.[51,54] A recent systematic review found that intermittent portal triad occlusion provides better protection against IRI in patients with chronic liver disease than does continuous portal triad occlusion.[55]

There are three main components of IRI.[56] The first concerns cellular activation; the second refers to the expression of adhesion molecules (Fig. 2), and the third to microcirculatory dysfunction. These are linked by various mediators including cytokines, chemokines, lipid mediators and complement factors. The mechanisms of IRI leading to cellular injury are summarized in Fig. 3.

In two RCTs involving, respectively, 66 and 60 patients and evaluating the effects of a synthetic protease inhibitor, gabexate mesilate, postoperative serum transaminases were markedly reduced, IL-6 production was suppressed and rates of postoperative complications were lowered.[57,58]

Ischaemic preconditioning is a process by which the liver develops increased protection against IRI through the release of adeno-

Figure 2 Role of adhesion molecules in ischaemia–reperfusion injury. ICAM-1, intercellular adhesion molecule-1; MAC-1, macrophage-1 antigen; MCP1, monocyte chemotactic protein-1; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; XDH, xanthine dehydrogenase; XOD, xanthine oxidase. References: [56,89–91]

sine, decreased endothelin-1 (ET-1) expression, altered nitric oxide synthase (NOS) induction, suppressed cytokine and free radical release, and transcriptional activation of stress genes, such as heat shock proteins, and adenosine triphosphate (ATP) preservation.[59–63] An increase in carbon monoxide is protective because it helps to maintain microvascular and portal blood flow by regulating NOS and vasodilation.[61] Studies show that the ultrastructure of parenchymal and non-parenchymal cells can be maintained even when the accumulated ischaemic duration with intermittent portal clamping is extended to 120 min.[64]

Efforts to improve hepatic tolerance of IRI have included the use of high-concentration glucose administered i.v. 24 h prior to surgery with the aim of increasing hepatocellular glycogen and ATP content.[65] Heizmann *et al.* found that improved hepatic macrocirculation (Table 3) in addition to hepatic microcirculation following ischaemic preconditioning offered protection against IRI.[66] A systematic review of RCTs discussing pharmacological interventions that aim to ameliorate IRI, many of which were small, individual, clinical studies, shows that none so far

demonstrate any clinical benefit.[67] Ischaemic preconditioning may be achieved surgically by exposing the liver to a brief period (often 10 min) of ischaemia followed by 10 min of reperfusion prior to a prolonged ischaemic period.[63] It is thought that the first period of portal clamping in the intermittent portal clamping method provides similar effects through a form of ischaemic preconditioning.[62] Ischaemic preconditioning also appears to have a protective effect when the selective hepatic vascular exclusion (SHVE) manoeuvre (with inflow and outflow occlusion) is applied.[68] However, the effects of ischaemic preconditioning under hepatic inflow occlusion in normal liver were not found to translate into significant reductions in mortality, liver failure, perioperative morbidity, hospital stay and ICU stay in a systematic review of five trials.[69] In addition, a systematic review of four RCTs comparing hemihepatic with total hepatic inflow occlusion reported no significant difference in the clinical outcomes of blood loss, transfusion requirement, mortality, morbidity, operating time and hospital stay.[70] In patients with livers at increased risk for the effects of ischaemia and reperfusion (cirrhotic, fibrotic or steatotic

Figure 3 Summary of mechanisms in ischaemia–reperfusion injury. IL-1, interleukin-1; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α. References: [56,89]

livers), the potential of the hemihepatic inflow occlusion approach remains to be explored.[70,71]

Liver regeneration

Liver regeneration is particularly significant in the context of major hepatic resections and small-for-size syndrome.[72] The elevation in portal pressure that results from extended liver resection causes excess shear stress on the remnant liver with a reduction in portal vein flow and ultimately impaired regeneration.[1,73] Much of the current understanding of physiological pathways in liver regeneration stems from extensive research in animal models.[72,74] There are few data on the precise timing of the processes involved in humans.[72] By contrast, the volumetric and functional recovery of the liver has been studied more extensively in patients following donor hepatectomy. In a series of 27 donors who underwent right hepatectomy, the remnant liver increased to 74% of its original volume at postoperative day 10 and continued to reach 83% of its original volume at 12 months.[75]

The liver will regenerate in response to loss of liver mass or liver function in order to restore functional liver volume.[72,76] A larger resection or greater tissue damage will result in an increased replication rate.[76] Proliferation of all liver cell types occurs, but non-parenchymal cells (endothelial, Kupffer and biliary duct cells) will have a more delayed course.[74] Cells undergo cell cycle reactions (G1–G1) until a liver mass matched to body size is restored.[72] Signalling pathways lead to an important G1–S transition in which liver cells commit to division and the time from G0 to S phase will depend on cell type.[72] The role of the 'oval cell compartment' originating from ductular cells in generating hepatocytes and bile duct cells post-hepatectomy has not been established as it has in toxic liver injury and other forms of liver damage.[72] Bone marrow-derived cells appear to contribute to further cellular resources capable of restoring liver mass.[77]

Table 4 Factors affecting regeneration following hepatic resection

Factors	Effect
Hepatic arterial buffer response	Same total portal flow through smaller hepatic volume carries hepatotrophic factors[72,78]
Hepatocyte injury	Increase in circulating cytokines, IL-6, TNF-α stimulates priming factors for cell cycle activation[72,78] Increased energy requirement triggers release of hepatocyte growth factor, TGF-α and epidermal growth factor[72,78]
Ischaemic preconditioning	There are few clinical data on the beneficial effects of ischaemia preconditioning on liver regeneration compared with IRI;[102] however, it has been shown to protect against IRI, which impairs liver regeneration following hepatectomy
Biliary obstruction	Reduces hypertrophy rate and regeneration following PVE or hepatectomy through a restricted portal venous flow caused by hepatic fibrosis, altered signalling pathways associated with regeneration, and an impaired enterohepatic circulation[78] Patients with obstructive jaundice treated by external biliary drainage prior to hepatic resection may have impaired liver regeneration as a result of the disruption of the enterohepatic circulation[79]
Diabetes	Patients with diabetes have reduced synthesis of RNA, DNA and protein on day 1 post-hepatectomy, as well as reduced hypertrophy caused by lack of insulin, a hepatotrophic factor[78]
Nutrition	Patients with malnutrition have decreased regeneration following hepatectomy and higher postoperative mortality as regeneration capacity depends largely on availability of energy[37,78,82] Enteral feeding will help to produce a better portal venous flow favouring regeneration[78] NASH has not been shown to affect liver regeneration, which shows over-nutrition probably has a small effect on regeneration capacity[78,103]
Cirrhosis	Recovery of lost cell mass is delayed and achieved incompletely, which is consistent with a higher risk for liver failure and mortality in the early postoperative period[82] A postoperative fall in hepatic ATP energy state is more sustained in cirrhotic liver[82] The normal liver will modulate energy metabolism or 'hepatic energy economy' in order to accommodate an increased metabolic load, but nonetheless develops a declined energy state around postoperative day 4, at the time when the liver reaches its maximal regenerative capacity, while curtailing its normal differentiated functions[81,82] This recovery process is delayed in cirrhotic liver and is probably related to its decreased flexibility in making economic adjustments post-hepatectomy[82]
Gender	The female gender may be more favourable towards regeneration as a result of the differential effects between the genders of sex hormones on regeneration[78]

ATP, adenosine triphosphate; IL-6, interleukin-6; IRI, ischaemia–reperfusion injury; NASH, non-alcoholic steatohepatitis; PVE, portal vein embolization; TGF-α, transforming growth factor-α; TNF-α, tumour necrosis factor-α.

Factors triggering or influencing hepatic regeneration are shown in Table 4. Insulin and other growth factors that facilitate hepatic regeneration are delivered via portal blood to the liver. Other factors, such as glucagons, transforming growth factor-β (TGF-β) and glucocorticoids will inhibit regeneration.[72] Signals of the cascade leading to proliferation are integrated to allow regeneration to occur in a synchronized fashion.[74] The signal for cells to return to G0 (quiescent phase) is unknown and may be related to TGF-β or activin, potent inhibitors of hepatocyte growth.[72] Impaired biliary drainage or biliary obstruction impedes liver hypertrophy and regeneration[78,79] (Table 4). Portal hyperperfusion and/or impaired venous outflow have been implicated in the failure of normal regeneration to occur in small-for-size syndrome.[5]

The increase in liver volume is an indicator of regeneration; computed tomography (CT) is an easy, non-invasive imaging modality for measuring liver volume.[79] However, volume restoration may be overestimated in CT as a result of postoperative vascular engorgement or oedema.[79,80] Nagino *et al.* found a poor correlation between regeneration measured by CT volumetry and postoperative liver dysfunction.[79] Liver volume may not accurately reflect the quantity of hepatocytes, especially in cirrhotic livers.[80] Galactosyl-human serum albumin scintigraphy (GSA) is a

method of estimating functional liver mass and was compared with CT liver volume in 32 patients undergoing liver resection.[80] Whereas volumetric regeneration reached 90% at 1 month,[75,80] 6 months were required for functional regeneration to reach the same level.[80] Surprisingly, functional gain in the diseased liver (chronic hepatitis or cirrhosis) was more rapid and more complete than volumetric recovery.[80]

Postoperative changes in phosphoester biochemistry or energy metabolism as detected by proton-decoupled 31P magnetic resonance spectroscopic imaging relate to the rate of liver regeneration.[81,82] The derangement in phosphoester metabolism is increased in cirrhotic liver following resection.[82] Zakian *et al.* showed that following the time course of the recovery of phosphoester metabolism may aid in making a clinical judgement of the appropriate timing for adjuvant chemotherapy.[81]

Pharmacological approaches to improve liver regeneration have so far mostly been investigated in animal studies.[74,83] In a double-blind RCT, pentoxifylline was found to improve the regeneration of small remnant livers (ratio of remnant liver to body weight: ≤ 1.2%) based on three-dimensional volumetry by magnetic resonance tomography at postoperative day 8. This effect was believed to have been mediated by IL-6.[83] However, morbidity and mortality outcomes did not differ significantly from those in the control

Table 5 Clinical recommendations and areas of future potential research in patients undergoing hepatic resection

Purpose	Clinical recommendation	Potential areas of research
Preoperative identification of patients at high risk for complications	Assessment and optimization of both function and volume of FLR	Standard definition of risk of FLR based on volume and functional status Development of predictive nomograms
Prevention of complications Intraoperative techniques	Optimization of comorbidity including cardiac, renal (Cr > 155 mmol/l) and metabolic[43,45,46]	
	In patients undergoing preoperative biliary drainage ensure bile is returned via enteric tract[78,79]	
	Cessation of hepatoxic agents (e.g. alcohol, chemotherapy) and period of recovery prior to surgery	Role of reversal of hepatic steatosis prior to hepatic resection
	In high-risk patients consider use of perioperative methyl prednisone[6,35,40,41]	Large multicentre RCT of steroids with well-defined group of patients at high risk for postoperative complications to determine if improvements occur in clinically significant endpoints
	Preoperative manipulation of the FLR in high-risk subgroups[78,85,86]	RCTs may not be ethically viable; using predictive nomograms and measuring variance may be a better solution
	In patients at high risk for small-for-size syndrome or impaired regeneration, consider use of 5 days of BCAA and human growth factor[84]	Determine role of manipulation of splanchnic blood flow either surgically or pharmacologically
	Avoid unnecessary invasive foreign bodies such as catheters, drains and i.v. lines	
	In patients at risk for AKI, ensure MAP remains at >80 mmHg[43,44] In patients in whom IRI is likely to result in an adverse outcome, adopt the following strategy:[40,51,54] Intermittent inflow occlusion Hemi-inflow occlusion[70,71] Use of gabexate mesilate[57,58] Period of ischaemic preconditioning[59–63]	Determine the efficacy of terlipressin in those with hepatorenal syndrome post-hepatic resection
Optimization of coagulation status	In patients undergoing extensive liver resection (>50%) consider: Real-time assessment and correction of coagulation deficits[12]	Further real-time physiological studies on changes to coagulation system as a whole and effect of correcting deficits on clinical outcomes
	Treatment with AT-3 if coagulation falls to <60% of baseline level[12]	Identification of optimal treatment to correct deficits (e.g. factor-specific or generic)
	Use of DVT prophylaxis as per international guidelines[14]	Identification of patients who benefit from prolonged DVT prophylaxis
Early postoperative identification of patients at risk for complications	In high-risk patients: Early assessment of predictors of PLF: (CRP < 32 mg/l at day 1, α-GST at >490 μg /l at 2 h postoperatively, lactate >4 mmol/l) Monitoring for AKI Early identification of sepsis: ↑ Bilirubin >day 7 ↑ CRP at day 3	Further clinical assessment to determine optimal variable and cut-off to determine optimal positive and negative predictive values
Treatment of complications	Aggressive management of suspected sepsis as per international guidelines[2,30]	
	Treatment of hypophosphataemia if <0.7 mmol/dl[16,18]	Determine if treatment of PO_{4-} improves clinical outcome
	Tight glucose control in perioperative period[24]	Determine optimal method of lowering serum ammonia
	Supplement nutrition with BCAA[26]	Determine if MARS has any clinical benefit in patients with PLF

AKI, acute kidney injury; AT-3, antithrombin-3; BCAA, branched-chain amino acids; CRP, C-reactive protein; DVT, deep venous thrombosis; FLR, future liver remnant; α-GST, α-glutathione S-transferase; IRI, ischaemic–reperfusion injury; MAP, mean arterial blood pressure; MARS, molecular adsorbents recirculation system; PLF, postoperative liver failure; RCT, randomized controlled trial.

group.[83] Luo *et al.* studied the effects of the provision of BCAA and recombinant human growth factor for 5 days on the remnant liver in 24 hepatocellular carcinoma (HCC) patients with liver cirrhosis and found improved recovery of liver function, protein synthesis and regeneration.[84]

Portal vein embolization (PVE) and two-stage hepatectomy represent two strategies which have been used in clinical practice to increase the volume of the future liver remnant (FLR) and reduce the risk for postoperative liver insufficiency. The reductions in postoperative mortality and morbidity following PVE in both healthy and diseased liver have been documented in many observational studies, although most of these were retrospective.[78,85,86] Portal vein embolization is usually considered when the FLR is estimated to be <25–35% of the whole liver in patients with a normal liver and <40% in patients with underlying parenchymal disease and patients who are undergoing preoperative chemotherapy.[86] The haemodynamic changes that occur after PVE are not as dramatic as those following partial hepatectomy and therefore activation of liver proliferation occurs less rapidly.[78] Despite this difference, hepatic regeneration occurs via similar mechanisms.[78]

After PVE, hepatic arterial flow to the embolized and non-embolized lobes increases via the 'hepatic arterial buffer response'.[1,78] Portal venous flow is diverted to the non-embolized lobe to maintain drainage from the splanchnic circulation.[1,78] The non-embolized lobe thus receives a total increase in blood supply, which results in hypertrophy, while the embolized lobe atrophies in response to its reduction in total blood supply.[78] The differentiated function of the embolized lobe is likely to be maintained.[78] Failure of the non-embolized lobe to regenerate after contralateral PVE is considered by some to be a risk factor for poor function of the FLR and a relative contraindication to proceeding with resection.[87] Dual embolization (PVE followed by arterial embolization) has been proposed as a method to further increase blood flow to the non-embolized lobe and thus to improve the hypertrophy rate.[78] A retrospective study comparing two-stage hepatectomy and PVE with one-stage hepatectomy in 43 hepatectomy patients with multiple bilobar colorectal metastases showed that the FLR hypertrophy ratio relative to pre-procedure volume in the two-stage group (50.2%) was twice that in the PVE group (25.3%).[88] However, the difference in longterm survival is unknown and a multi-institution prospective study of two-stage hepatectomy is yet to be carried out.

Discussion
Limitations

Because of the breadth of the current review, the range of study types and the essentially descriptive nature of much of the information reviewed, no assessment of bias or the grade quality of individual studies was performed in this review. In addition, because of the lack of high-level evidence, no objective grading was performed for any specific intervention; however, Table 5 provides a narrative description of potential interventions and

considers areas for further research. The literature search was limited to English-language studies within the search period and included less recent papers that remain highly relevant. Because of the wide range of subtopics, it is possible that some relevant literature may not have been identified by the electronic search strategy. Therefore, any landmark studies or other relevant studies identified through hand-searching were considered for their eligibility for inclusion.

Conclusions

Patients undergoing liver resection incur pathophysiological consequences which relate to hepatocellular injury and reduced hepatic mass. Most patients undergo rapid regeneration, but in some the residual mass is either insufficient or regeneration is disordered and these patients are at risk for PLF and other associated complications. These changes are influenced by preoperative factors including liver parenchymal disease, patient age and comorbidities, intraoperative factors including the extent of resection, blood loss and ischaemia, and postoperative factors such as sepsis and other systemic complications. The recognition of any deviation from the expected path to recovery is important because although there is limited high-level evidence for specific treatment modalities for PLF, patients require careful and vigilant supportive care through a prolonged recovery phase. Most interventions tested to date have not been found to have conclusive effects on morbidity and mortality. However, further research and attention to clinical factors and their pathophysiological effects following liver resection may help to improve patient selection, inform the choice of procedure, and recognize and deal with complications at an early stage.

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