Review

JOURNAL OF HEPATOLOGY

# Liver resection for cancer: New developments in prediction, prevention and management of postresectional liver failure

Kim M.C. van Mierlo[1], Frank G. Schaap[1], Cornelis H.C. Dejong[1,2], Steven W.M. Olde Damink[1,3,*]

## Summary

Hepatic failure is a feared complication that accounts for up to 75% of mortality after extensive liver resection. Despite improved perioperative care, the increasing complexity and extensiveness of surgical interventions, in combination with an expanding number of resections in patients with compromised liver function, still results in an incidence of postresectional liver failure (PLF) of 1–9%. Preventive measures aim to enhance future remnant liver size and function. Numerous non-invasive techniques to assess liver function and predict remnant liver volume are being developed, along with introduction of novel surgical strategies that augment growth of the future remnant liver. Detection of PLF is often too late and treatment is primarily symptomatic. Current therapeutic research focuses on ([bio]artificial) liver function support and regenerative medicine. In this review we discuss the current state and new developments in prediction, prevention and management of PLF, in light of novel insights into the aetiology of this complex syndrome.

**Lay summary**: Liver failure is the main cause of death after partial liver resection for cancer, and is presumably caused by an insufficient quantity and function of the liver remnant. Detection of liver failure is often too late, and current treatment focuses on relieve of symptoms. New research initiatives explore artificial support of liver function and stimulation of regrowth of the remnant liver.


Keywords: Postresectional liver failure; Liver resection; Hepatic cancer; Liver regeneration; Review.

*Received 19 February 2016; received in revised form 3 June 2016; accepted 7 June 2016*

## Introduction

Partial liver resection for hepatobiliary tumours is relatively safe and often the only curative treatment option. The unequalled capacity of the liver to regenerate and restore its functionalities permits the surgical removal of a substantial part of the liver mass. However, postresectional liver failure (PLF) occurs in up to 9% of patients and remains the main cause of postoperative mortality [1,2]. PLF has a subacute course, and an inadequate functional reserve of the remnant liver is central in its aetiology. Insufficient hepatic secretory capacity is reflected by hyperbilirubinemia, whereas decreased synthetic and detoxifying functions can manifest as coagulopathy and hepatic encephalopathy [1].

Hyperbilirubinemia is included in all currently used definitions of PLF. The '50–50 criteria' predict a 59% risk on early postoperative mortality if systemic bilirubin rises above 50 μmol/L and prothrombin time decreases to 50% on postoperative day 5 [3]. The 'peak bilirubin criterion' defines PLF as a bilirubin level above 120 μmol/L within 90 days after major hepatectomy, and has a positive predictive value of 33% for liver-related death in non-cirrhotic patients [4]. The definition of PLF developed by the International Study Group of Liver Surgery encompasses bilirubin elevation (according to local criteria) on or after postoperative day 5, and grades PLF based on international normalized ratio (INR) derangement [5]. Postoperative mortality in PLF grade A (INR <1.5), B (INR ⩾1.5 and <2.0) and C (INR ⩾2.0) was 0%, 12%, and 54%, respectively [5]. In order to provide a comprehensive overview of this syndrome, no specific definition was selected for this review.

[1]*Department of Surgery, Maastricht University Medical Centre & NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands*;
[2]*GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands*;
[3]*Department of Surgery, Institute of Liver and Digestive Health, Royal Free Hospital, University College London, London, United Kingdom*

**Key point**

Postresectional liver failure (PLF) is the main cause of postoperative mortality after liver resection for hepatobiliary malignancy.

*Abbreviations:* PLF, postresectional liver failure; INR, international normalized ratio; RLV, remnant liver volume; CALI, chemotherapy-associated liver injury; CRLM, colorectal cancer liver metastasis; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; SOS, sinusoidal obstruction syndrome; NRH, nodular regenerative hyperplasia; SD, sinusoidal dilatation; ALP, alkaline phosphatase; ICG-R15, indocyanine green retention rate after 15 min; APRI, AST-to-platelet-ratio index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MR, magnetic resonance; CT, computed tomography; TE, transient elastography; MRE, magnetic resonance elastography; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; PVE, portal vein embolization; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; FXR, Farnesoid X Receptor.

**Key point**

Insufficient remnant liver volume and function are central in the aetiology of PLF, and detailed assessment of preoperative liver function is pivotal in surgical management of hepatobiliary tumours.

* Corresponding author. Address: Universiteitssingel 50, H5.485, 6229 ER Maastricht, The Netherlands. Tel.: +31 43 3881497.
*E-mail address:* steven.oldedamink@maastrichtuniversity.nl (S.W.M. Olde Damink).

## Liver regeneration after partial liver resection

Liver regeneration following partial hepatectomy is a tightly orchestrated process involving the spatiotemporal interplay between parenchymal and non-parenchymal cells and is driven by multiple signals (see for detailed reviews references [6,7]). First, immediately after partial liver resection, the total hepatic inflow passes through the vascular bed of the smaller remnant liver. Resultant shear stress, a relative increase in supply of signalling molecules from the (portal) circulation, and growth factors released after remodelling of the extracellular matrix, provide the triggers for initiation of liver regeneration. Interleukin 6 and tumour necrosis factor alpha released by activated Kupffer cells are important for cell cycle re-entry of normally quiescent hepatocytes, with further cell cycle progression driven by mitogens such as hepatocyte growth factor. Proliferation of the various non-parenchymal cell types enables re-establishment of the hepatic architecture. Through poorly understood molecular events, liver regeneration terminates when the original liver mass and functional capacity have been restored.

## Aetiology of postresectional liver failure

During liver regeneration, a minimum amount of remnant liver is required to maintain vital liver functions and support regrowth. In a seminal study almost half of the patients with a remnant liver volume (RLV) smaller than 26.6% of the pre-resection value, developed severe hepatic dysfunction compared with 1.2% of patients with a larger RLV [2]. Consequently, a RLV of 25–30% is currently used as lower limit in patients with normal liver function, whereas a minimum RLV of about 40% is mandatory in patients with impaired liver function [8]. Five main factors have been recognized in the aetiology of PLF (Fig. 1).

### *Hepatic haemodynamic imbalance*

PLF shares features of the small-for-size syndrome that occurs in the setting of (partial) liver transplantation. Portal hyperperfusion of the remnant liver results in adaptive reduction of arterial blood flow through activation of the hepatic arterial buffer response (see reference [9] for a detailed review). While increased perfusion and resultant shear stress are instrumental in initiating the regenerative cascade, portal hyperperfusion and arterial hypoperfusion may have deleterious effects on postoperative recovery of liver function [9]. Increased portal flow and pressure after major hepatectomy increased the risk for PLF in non-cirrhotic patients [10]. In patients undergoing partial liver transplantation, post-reperfusion portal hypertension resulted in sinusoidal damage and reduced levels of nitric oxide, a signal molecule engaged in the initiation of liver regeneration [11].

### *Unmet hepatic metabolic demand: disturbed bile salt homeostasis*

Impaired activity of the canalicular pump(s) involved in bilirubin secretion results in intrahepatic accumulation and systemic release of conjugated bilirubin [12]. While bilirubin is generally not regarded as detrimental to the liver, a more generalized dysfunction of canalicular transporters may result in hepatic accumulation of bile salts. Circulating levels of bile salts rise as early as one minute after partial hepatectomy in rats [13], and this is shortly followed by transient accumulation of bile salts in the liver [14]. An important stimulatory role for bile salts and their membrane-bound and nuclear receptors in liver regeneration is emerging [15]. Being biological detergents, excessive intracellular accumulation of bile salts, however, causes damage to internal membranes (particularly in mitochondria) of the hepatocyte and results in apoptosis [16]. In mice with deranged bile salt homeostasis, otherwise well-tolerated 70% partial hepatectomy results in massive hepatocyte necrosis and early mortality [17]. Animal studies underscore that tight control of (hepatic) bile salt homeostasis is a prerequisite for unimpeded liver regeneration [17,18].

### *Impaired liver innate immune defence*

Liver regeneration after partial hepatectomy involves activation of the livers' innate immune system [19]. Innate immune receptors of the Toll-like receptor family that recognize bacterial products, and downstream (adaptor) proteins that relay the signal intracellularly, are engaged in this activation step [20]. Liver-resident macrophages not only play an important role in the regenerative response after liver resection by producing priming factors, they also clear portal endotoxins and eliminate translocated bacteria [21], thus limiting exposure of hepatocytes to (pro-apoptotic) lipopolysaccharide (LPS) and preventing systemic infection [22]. Following resection, adequate numbers of Kupffer cells should remain to preserve these essential functions. The risk of infection increases with the extent of resection, and a majority of patients with hepatic dysfunction also develops infectious complications [2]. Cytokine release by activated Kupffer cells is hampered after major liver resection [22]. Likewise, impaired phagocytic activity of the reticuloendothelial system is observed after major resection [23], and this likely contributes to increased infectious risk [2].

### *Gut microbiome-gut-liver axis*

An emerging concept is that the gut microbiota modulates the regenerative ability of the liver

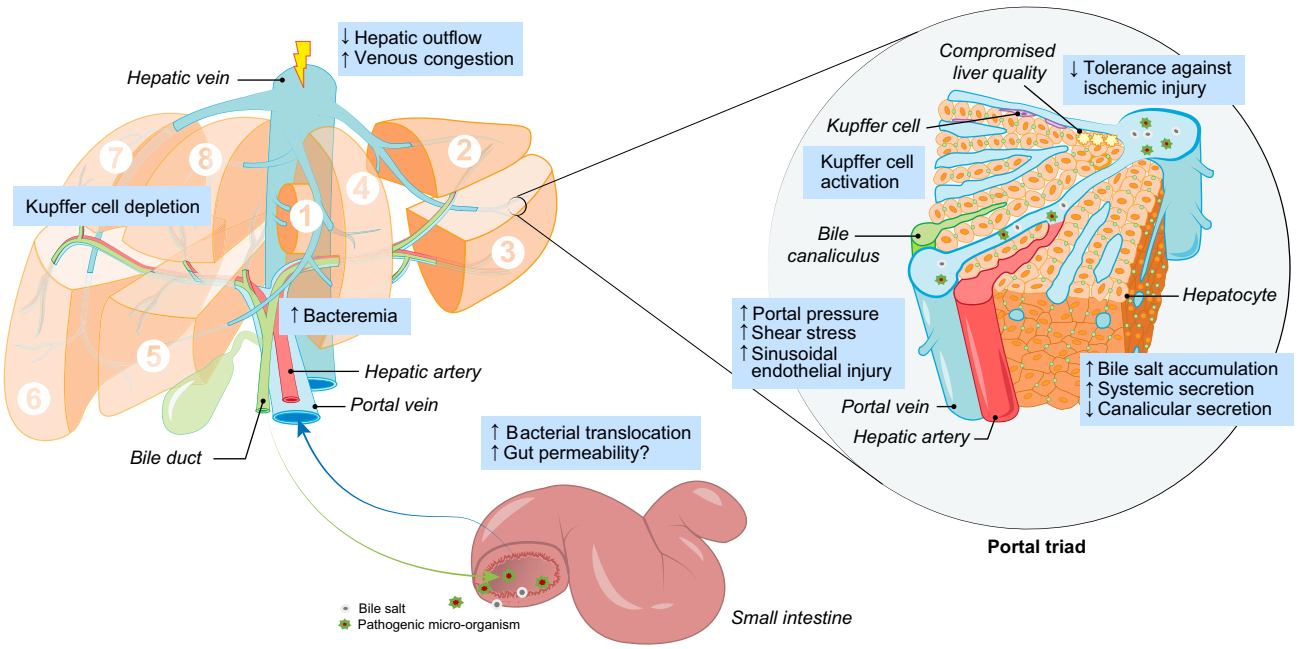


**Fig. 1. Aetiology of postresectional liver failure.** The altered blood-to-liver volume ratio causes elevated portal pressure and resultant shear stress and sinusoidal endothelial injury. Although Kupffer cells are activated, activity in the liver remnant is inadequate to initiate and/or maintain the innate immune response that drives postresectional liver regeneration. Combined with increased enteric bacterial translocation, the infectious risk is increased. Impaired canalicular secretion of bile salts results in intrahepatic accumulation and subsequent hepatocellular injury. In case of venous reconstruction, impaired hepatic outflow can result in hepatic venous congestion. Lastly, livers with compromised function due to chronic liver diseases are more vulnerable to perioperative ischemic reperfusion injury, as reflected in impaired recovery of postoperative liver function.

(reviewed in reference [24]). This is likely to involve interactions between the gut microbiome and host metabolism, effects of the gut microbiota on bile salt physiology, as well as effects of bacterial endotoxins [24,25]. Bile salts exert direct antimicrobial activity and shape the composition of the gut flora. Conversely, certain microbial strains can convert the host's primary bile salts into secondary species, thus affecting the signalling properties of bile salts. This again can impact host metabolism, bile salt homeostasis, and liver regeneration [26–28]. As discussed above, activation of the innate immune response in the liver is important for liver regeneration after partial hepatectomy, and microbial products including LPS are implicated in Kupffer cell activation [29]. Failure of gut-derived endotoxins to reach the liver resulted in impaired DNA synthesis in replicating hepatocytes, likely through reduced production of priming factors [30]. On the other hand, excessive levels of endotoxin can impair liver regeneration and cause mortality after extended hepatectomy.

*Impaired background liver function*

Impaired liver quality plays a pivotal role in PLF and is frequently present in patients that undergo partial hepatectomy for the three most common indications: colorectal cancer liver metastasis (CRLM), hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Four types of liver pathology are related to these hepatobiliary tumours, *viz.* chemotherapy-associated liver injury, fatty degeneration, fibrotic progression, and cholestasis.

## Chemotherapy-associated liver injury (CALI)

**Key point**

Four types of parenchymal dysfunction (chemotherapy-associated liver injury, fatty degeneration, fibrosis and cholestasis) are increasingly observed.

Neoadjuvant chemotherapy is widely used for downstaging of CRLM. Oxaliplatin is central in most currently used regimens and is considered the main causative agent for development of sinusoidal obstruction syndrome (SOS) and nodular regenerative hyperplasia (NRH), whereas irinotecan has been associated with the development of chemotherapy-associated steatohepatitis.

*Sinusoidal obstruction syndrome*

SOS is seen in up to 80% of patients undergoing oxaliplatin-based chemotherapy [31], and is characterized by injury of endothelial cells, parenchymal damage, and (fibrotic) venular lesions. Sinusoidal dilatation (SD) is the most common manifestation of SOS in the grading system of Rubbia-Brandt *et al.* [31].

Although exact mechanisms are unclear, a diminished preoperative functional reserve and longer hospital stay after major hepatectomy was reported in patients with SD [32]. The effect of SD on development of PLF is uncertain. Studies indicate no effect, or an incidence of PLF in up to 21% of patients with moderate to severe SD after major hepatectomy (0–4.2% in patients with absent or mild SD) [33,34]. Rodent models using monocrotalin or oxaliplatin to induce SOS revealed impairment of liver regeneration and induction of liver injury following partial hepatectomy [35]. This was accompanied by less pronounced induction of hepatic mitogens, reduced liver volume recovery, enhanced hepatocellular necrosis and higher serum alanine aminotransferase (ALT) and bilirubin levels [35,36].

Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor A, decreased the incidence of SD in patients that received oxaliplatin-based chemotherapy [37]. Downregulation of matrix metallopeptidase-9, a fibrotic remodelling factor involved in perisinusoidal extracellular matrix breakdown, may be accountable [38].

SD is a histological diagnosis and can be detected by biopsy, however the false-negative classification is high due to the spatial heterogeneity of its manifestation [34]. Surrogate measures are biochemical assessment, functional tests, imaging and spleen size measurement. Increased aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels can point to SD, but are non-specific. An indocyanine green retention rate after 15 min (ICG-R15) >10% and the preoperative AST-to-platelet-ratio index (APRI) are both independently associated with the presence of SD [32,33]. Patients with SD often have an increased spleen volume [39], with an increase of $\geqslant$30% reported to be predictive of SD [40]. Another typical SD-related abnormality seen in imaging is reticular hypointensity that presumably reflects locally impaired Kupffer cell function [41]. Superparamagnetic iron oxide-enhanced MRI can detect moderate to severe SD [41], but gadoxetic acid-enhanced MRI seems superior with a specificity of 96–100% on hepatobiliary phase images [42].

*Nodular regenerative hyperplasia*

A second histological characteristic of SOS is NRH, which is observed in over 24% of patients after oxaliplatin-based chemotherapy [38]. NRH is characterized by diffuse transformation of liver parenchyma into regenerative nodules that compress the surrounding parenchyma, and is graded according to Wanless *et al.* [43]. NRH probably arises due to changes in intrahepatic sinusoidal or portal blood flow [43].

The incidence of PLF is increased in patients with NRH, even rising to 25% after major hepatectomy in patients with moderate to severe NRH [44]. Furthermore, coexistence of NRH with moderate to severe SD has been noted [44]. Since SD, in contrast to NRH, was no indisputable risk indicator for postoperative outcome, it was suggested that NRH is the true determinant of poor short-term outcome after liver resection. Although the mechanism is not elucidated, hepatic injury, portal hypertension and a lower platelet count may predispose to PLF [45].

A decreased platelet count combined with elevated ALP, gamma-glutamyltransferase (GGT), and total bilirubin levels can be found in NRH [46]. APRI can predict NRH [44]. Percutaneous or transjugular liver biopsy with hepatic venous pressure gradient measurement may be used as a diagnostic tool, but should solely be applied in selected high-risk patients [44]. Reversibility of histological features is uncertain and bevacizumab seems to protect against development of NRH [38].

*Chemotherapy-associated steatohepatitis*

Irinotecan is associated with chemotherapy-induced steatohepatitis with widely ranging incidence reported in literature [47], and steatohepatitis after irinotecan proved to increase the risk of death from PLF [48]. Histopathological findings, prediction and prevention will be discussed below in conjunction with steatosis/steatohepatitis.

## Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

The prevalence of non-alcoholic fatty liver disease (NAFLD) in the adult Western population is approximately 20–30% and around 3–5% of adults are estimated to have non-alcoholic steatohepatitis (NASH) [49]. Despite lack of absolute consensus [50,51], steatosis and NAFLD seem to be risk factors for PLF and higher overall postoperative morbidity and mortality [2,52,53].

Rodent models show that vulnerability of the steatotic liver may be due to reduced tolerance against ischemic injury caused by decreased perfusion of the liver [54]. In addition, mitochondrial dysfunction in NAFLD results in impaired ATP synthesis, while Kupffer cell dysfunction increases reactive oxygen production which causes hepatocellular injury [54,55]. In the steatotic liver the ability of hepatocytes to regenerate after major tissue loss is impaired [56]. Multiple pathways contribute to unresponsiveness of fatty hepatocytes to regenerative stimuli, and subsequent cell cycle arrest [57]. Furthermore, cell cycle transition may be negatively affected by disturbed energy homeostasis in the fatty liver [55].

Biopsy remains the most reliable method for assessment of NAFLD but is increasingly replaced by non-invasive alternatives due to a small risk for

complications and sampling errors [58,59]. Non-invasive methods consist of functional liver tests, breath tests, imaging, and biomarkers that assess steatosis and fibrosis. The majority of patients with NAFLD have normal liver function tests, however some have elevated ALT, AST, GGT, and/or serum ferritin. Ultrasonography is still the imaging modality of choice in patients with >33% parenchymal steatosis, but its accuracy decreases in obese patients [60]. Magnetic resonance (MR) imaging (MRI) and MR spectroscopy directly quantify fat and outperform computed tomography (CT) and ultrasonography for prediction of steatosis when the fat content is >5.5% [61].

Transient elastography (TE) and MR elastography (MRE) indicate fibrosis by measuring liver stiffness. TE predominantly detects cirrhosis [62], and MRE can distinguish advanced from mild fibrosis [63]. Especially TE is easily applied in clinic but its use is limited by obesity, although utilization of an XL-probe improves accuracy in obese patients [64].

Simultaneous measurement of steatosis and fibrosis can be accomplished by integration of the controlled attenuation parameter in TE or acoustic radiation force impulse in a conventional ultrasonography machine [65,66]. Serum fibroblast growth factor 21 (Fgf21) and cytokeratin 18 are biomarkers that can discriminate between NASH and NAFLD [67,68], and NAFLD, NASH and fibrosis [67,68]. The fibrosis-4 score showed a negative predictive value of 98% for detecting patients without advanced fibrosis [69]. Other combined parameters that assess hepatic fibrosis are the APRI, FibroMeter NAFLD, NAFLD fibrosis score, and BARD score [70–73].

## Fibrosis and cirrhosis

Hepatic fibrosis is mainly present in patients undergoing partial liver resection for HCC, and is mostly caused by progression of steatosis or related to chronic viral hepatitis [74]. In the past, the decreased regenerative capacity of the fibrotic liver increased the risk of PLF and caused postoperative mortality rates of around 15% [75]. Present mortality rates have declined to 0–5% due to advances in preoperative liver function assessment and strict patient selection [74] (Fig. 2).

Little is known about the influence of fibrosis on PLF. Regeneration of the fibrotic liver is suggested to be a progenitor cell-mediated process, in contrast to replication of existing mature hepatocytes in the non-compromised liver [76]. Animal studies indicate that impaired regeneration and subsequent hepatic dysfunction following partial liver resection are due to inefficient induction of cell cycle transition mediators, hepatocyte necrosis, and a pronounced fibrogenic response [76,77]. Enhanced bacterial translocation and decreased innate and adaptive immune system activity add to vulnerability of the fibrotic liver as shown in animal and human studies [78].

For diagnostic purposes, percutaneous biopsy is increasingly replaced by four-pass transjugular biopsy [79], which provides the advantage of concurrent measurement of the hepatic venous pressure gradient (HVPG). Class I biomarkers (e.g., AST) reflect activity of fibrogenesis, whereas class II biomarkers (e.g. APRI) correlate with fibrosis [80]. TE is the most applied technique, but shows low accuracy in patients with obesity or ascites [81]. Both TE and acoustic radiation force impulse have high accuracy for assessment of cirrhosis [81]. Additionally, multiple combination serum tests, such as the FibroTest, Hepascore, and FibroMeter, are used with or without TE [82]. Gadolinium-enhanced MRI is promising as it showed significant signal intensity differences between patients with and without fibrosis [83].

Two preoperative parameters that directly predict development of PLF in patients with cirrhosis are an RLV-to-body weight ratio <1.4% [84] and the change in portal venous pressure [85]. Furthermore, whereas portal hypertension ought to be a contraindication for hepatic resection in patients with HCC, a recent study on the relationship between the HVPG and the development of PLF found that even in patients with a pressure gradient $\geqslant$10 mmHg, one-quarter of the patients experienced an uneventful postoperative course [86].

## Cholestasis

Obstructive cholestasis is characterized by retention of biliary constituents and a ductular reaction, and upon longer duration by hepatocyte degeneration, bile salt stasis, and progression of the ductular reaction to biliary fibrosis [87]. Patients with perihilar CCA often present with jaundice, weight loss, and cholangitis, whereas intrahepatic CCA is frequently associated with a silent clinical course and general symptoms such as malaise and loss of appetite resulting in late detection [88].

After extensive resection for perihilar CCA, PLF is seen in up to 30% of patients and mortality occurs in around 8–12% of patients [89,90], possibly due to a combination of cholangitis and a small RLV [91]. A complication rate of up to 38% is reported after surgical removal of intrahepatic CCA, with few patients developing PLF and a mortality rate of approximately 1% [92].

Animal studies suggest that biliary dilatation caused by distal obstruction compresses the portal triad resulting in a decreased portal flow with subsequent compensatory increased arterial flow in combination with portosystemic shunting (reviewed in reference [93]). Additionally, the interrupted enterohepatic circulation, lower expression of proliferative mediators in the priming and early

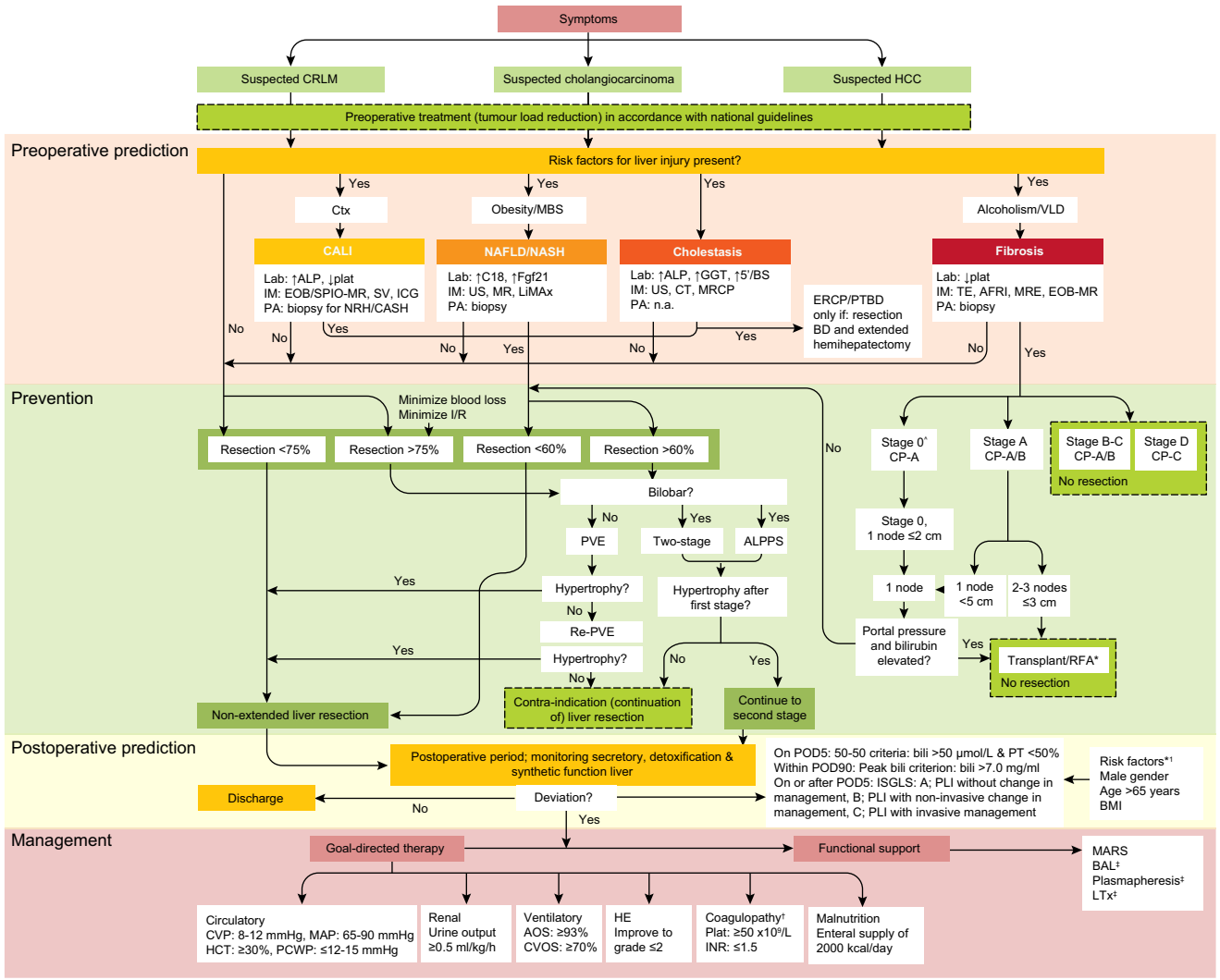


**Fig. 2. Flow chart for decision-making in liver surgery.** 5′,5′-nucleotidase; AFRI, acoustic radiation force impulse imaging; ALP, alkaline phosphatase; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; ALT, alanine transaminase; AOS, arterial oxygen saturation; AST, aspartate transaminase; BAL, bio-artificial liver; bili, total bilirubin; BD, bile duct; BMI, body mass index; BS, bile salts; C18, cytokeratin 18; CALI, chemotherapy-associated liver injury; CASH, chemotherapy-associated steatohepatitis; CP, Child-Pugh; CPV, central venous pressure; CRLM, colorectal liver metastases; CT, computed tomography; Ctx, chemotherapy; CVOS, central venous oxygen saturation; EOB, gadoxetic acid-enhanced; ERCP, endoscopic retrograde cholangiopancreatography; Fgf21, fibroblast growth factor 21; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HCT, hematocrit; HE, hepatic encephalopathy; I/R, ischemia-reperfusion injury; ICG, indocyanine green clearance; IM, imaging; INR, international normalized ratio; ISGLS, International Study Group of Liver Surgery; Lab, laboratory findings; Ltx, liver transplantation; MAP, mean arterial pressure; MARS, molecular absorbent recirculation system; MBS, metabolic syndrome; MR, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NRH, nodular regenerative hyperplasia; PA, pathology; PCWP, pulmonary capillary wedge pressure; plat, platelets; PLI, postoperative liver insufficiency; POD, postoperative day; PT, prothrombin time; PTBD, percutaneous transhepatic biliary drainage; PVE, portal vein embolization; Re-PVE, recurrent portal vein embolization; RFA, radiofrequency ablation; SPIO, superparamagnetic iron oxide-enhanced; SV, splenic volume; TE, transient elastography; US, ultrasonography. ^Barcelona clinic criteria *Resection criteria are expanded and presumably differ between centres; †in case of bleeding; ‡only tested pre-clinically or in acute liver failure/acute-on-chronic liver failure.

phase of regeneration, and toxic bile-associated hepatocyte apoptosis, add to defective regeneration after partial resection of the obstructed liver in rodents [93]. A significant suppression of mitotic indices and lower hepatic weight gain after partial hepatectomy is observed in cholestatic rats [94]. Furthermore, animal studies provided evidence for enhanced susceptibility to post-ischemic reperfusion injury in cholestatic rats [95]. The detrimental role of Kupffer cells in cholestatic injury is demonstrated by amelioration of injury in bile duct-ligated mice with prior depletion of Kupffer cells [96]. Moreover, an excessive inflammatory response through pro-inflammatory cytokine production led to deterioration of hepatic function after bile duct ligation, resulting in enhanced susceptibility to infection [97]. Jaundiced patients undergoing laparotomy additionally showed significantly more bacterial translocation [98]. This is in line with the high clinical incidence of postoperative infectious

complications in cholestatic patients undergoing partial hepatectomy [90].

Obstructive cholestasis is biochemically characterized by elevated serum bilirubin, ALP and GGT levels [99]. Inflammatory parameters are elevated in case of acute cholangitis [100]. Imaging of cholestatic parenchyma using ultrasonography, CT or MR cholangiopancreatography is not focused on assessing quality but on detection of dilated intrahepatic bile ducts.

### Assessment of liver volume and function

Both assessment of liver volume and function is mandatory to predict postoperative functional reserve. Methods for measurement of future RLV range from 2D volumetry on computed tomography, to perioperative 3D modelling. Computational software allows manual or automatic delineation of the liver on all CT or MRI sections, thereby allowing calculation of liver volume [101,102].

Liver function can be estimated by preoperative biochemistry, breath tests and imaging. Hepatic secretory (bilirubin), synthetic (INR) and detoxifying (ammonia) functions and liver damage (ALT, AST) are evaluated by clinical chemistry. Metabolic liver function testing can be performed with the LiMAx test and the indocyanine green clearance rate (ICGR-15) [11,12]. The LiMAx test measures metabolism of intravenously injected $^{13}$C-labeled methacetin in exhaled breath. Imaging techniques used in the clinic include $^{99m}$Tc-labeled galactosyl serum albumin (GSA) liver scintigraphy, $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy with single-photon emission computed tomography (SPECT), and gadolinium-enhanced MRI using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) [103–105]. Impaired enhancement of labeled contrast indicates decreased hepatic uptake and reflects compromised liver quality. Liver enhancement in gadolinium-enhanced MRI shows good correlation with regional liver function, and offers the advantage of simultaneous diagnostic evaluation and functional assessment [104].

### Prevention of postresectional liver failure

Prevention of PLF consists of four principles: optimizing preoperative liver function, enlarging RLV, limiting hepatic haemodynamic disbalance and providing optimal perioperative care.

#### *(Pre-)clinical methods of preoperative liver optimization*

The liver of patients with SOS is in a prothrombotic state as reflected by upregulation of plasminogen activator inhibitor-1, Von Willebrand factor and factor X [106]. The fibrinolytic agent defibrotide is administered in bone marrow transplant recipients for treatment of SOS [107], and might be beneficial in chemotherapy-related SOS as well. Anti-platelet therapy such as aspirin seems to protect against oxaliplatin-induced SOS in patients [108]. Oxaliplatin is conjugated to glutathione and subsequently excreted from the cell, which is the probable cause of reduced hepatic glutathione levels seen in SOS [106]. Supplementation of antioxidant therapy (hydroxyanisole) or flavonoids reduced the severity of sinusoidal injury in rodents [106,109]. This effect has not yet been confirmed in humans. Chemotherapy-free interval prior to liver resection may reverse SOS, as suggested by a longer period since the last cycle of chemotherapy in patients without histological evidence of SD at the time of liver resection [32]. On the other hand, hepatic sinusoidal lesions and even progression of fibrosis are reported up to several months after cessation of chemotherapy [31]. Portal hypertension can be diminished by perioperative splenic artery ligation in patients with severe NRH and portal hypertension, and might decrease postoperative morbidity [110].

Liver steatosis can be reduced by a preoperative very-low calorie diet, as has been shown in potential liver transplant donors [111]. Less steatosis and steatohepatitis was observed in patients with one week of calorie restriction prior to resection for benign or malignant liver disease, compared to *ad lib* fed patients [112]. However, despite less intraoperative blood loss in the diet group, no effect was seen on postoperative complications in this patient group.

Optimization of liver function in patients with cirrhosis has not yet been attempted, however, platelet infusion may be an option. Thrombocytopenia in cirrhosis may be caused by a decrease in (hepatic) thrombopoetin production and systemic removal of platelets in the spleen [113]. Platelets have a stimulatory effect on liver regeneration [114], and platelet infusion might provide an option for preoperative optimization.

The preventive role of preoperative biliary drainage in obstructive cholestasis is uncertain. Internal (stenting via endoscopic retrograde cholangiopancreatography, ERCP) or external (percutaneous transhepatic biliary drainage, PTBD) drainage in pancreatic head cancer patients has been shown to have no benefits on surgical outcome and induced drainage-related complications [115], whereas its role in proximal malignant bile duct obstruction is inconclusive. Preoperative improved secretory liver function, improved postoperative liver regeneration, and a reduction of mortality after right hemihepatectomy were reported [116], but this could not be reproduced by others [117,118]. Drainage-related complications such as cholangitis and haemorrhage are seen in up to 33% of patients [116]. Especially infectious complications are more

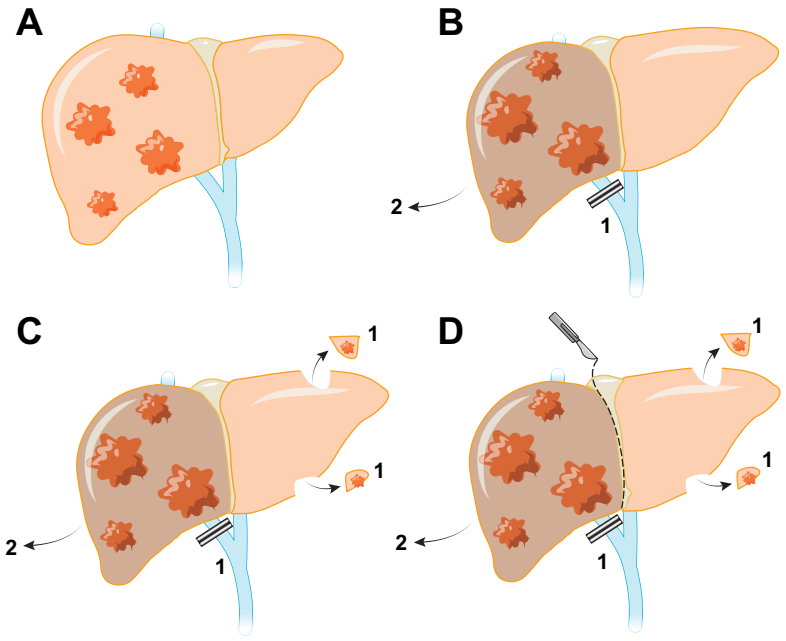


**Fig. 3. Visualization of pre- or perioperative interventions and their effect on liver remnant volume.** (A) Malignant liver disease (B) Embolization/ligation of the right portal branch (1) results in atrophy of the right hemi-liver and compensatory growth of the left hemi-liver, which can be removed when appropriate hypertrophy has been achieved (2). (C) Removal of tumours from the left hemi-liver and occlusion of the right portal branch (1). After 4–6 weeks, the volume of the left hemi-liver is increased and the right hemi-liver can be removed (2). (D) Removal of tumours from the left hemi-liver, *in situ* splitting of the hemi-livers, and simultaneous ligation of the right portal vein branch (1). After one week, augmented hypertrophy of the left hemi-liver permits removal of the right hemi-liver (2).

frequent after ERCP stenting [119], whereas PTBD causes interruption of the enterohepatic cycle and impairment of liver regeneration [15]. Bile salt reinfusion during PTBD had beneficial effects on postoperative liver function [120].

*Enlarging of future remnant liver volume*

Hypertrophy-inducing procedures and surgical adaptations should be performed if the RLV is expected to be <25% in patients without liver disease and <35–40% in patients with impaired liver function [8]. In general, portal vein embolization (PVE, Fig. 3) enlarges the RLV with approximately 35–40% and improves eligibility for hepatectomy by 20% [1]. In less than 5% of patients the hypertrophic response following PVE is inadequate [121]. Major PVE-related complications occur in approximately 2.5% of patients and include intra-abdominal abscess, liver hematoma, and backflow of embolization material [121]. A recent meta-analysis comparing PVE with ligation of the portal vein (PVL) showed comparable preoperative hypertrophic responses and postoperative morbidity [122]. New developments exist of polyvinyl alcohol particles with plugs or coils as embolizing materials, and have resulted in lower recanalization rates, enhanced hypertrophy, and a decreased occurrence of PLF [123].

**Key point**

Treatments to enhance liver regeneration may enlarge the number of patients eligible for curative intent surgery.

Disease progression after PVE occurs in up to 66% of patients, and is likely due to increased arterial flow to the embolized lobe and/or waiting period to surgery [124]. The interval between PVE and surgery should therefore be as short as possible but not less than 2–3 weeks [124]. Post-PVE chemotherapy before resection may halt disease progression without affecting subsequent liver regeneration [125].

PVE is commonly performed after the administration of chemotherapy [108]. Evidence for the influence of CALI on post-PVE hypertrophy is conflicting. Whereas SD seems to have a clear inhibitory effect on hypertrophy [126], chemotherapy has no effect on liver regrowth [121,127]. Moreover, patients with NASH show a trend towards less post-PVE liver volume gain compared to patients with normal liver function [126]. Although robust evidence is lacking [121], cholestasis appears to have no negative impact on hypertrophy after PVE. After right hepatectomy in patients with chronic liver disease, PLF developed in 50% of patients without PVE *vs.* 7.1% in patients with PVE [128]. Impaired hypertrophy after technically successful PVE in patients with chronic liver disease is a contraindication for major resection [128].

The two-staged hepatectomy is an excellent method to increase RLV and consequently achieve curation in patients with bilobar tumours, who are not deemed resectable in one attempt. PVL concurrent with two-stage hepatectomy resulted in an RLV gain of about 50–60% after four weeks. This strategy is advised in case of an RLV after the first stage of <25–30% and <40% in patients without and with chronic liver disease, respectively. Liver cirrhosis is a contraindication for the two-staged procedure.

The recently developed associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure is based on the same principle as two-stage hepatectomy, albeit that during the first stage in ALPPS the liver is split *in situ* combined with portal vein ligation, and the second stage consists of removal of the ligated lobe 7–14 days later [129]. An astonishing average hypertrophy rate of 80% can be achieved with this procedure, creating a curative opportunity for initially non-resectable patients who have insufficient hypertrophy on PVE [130]. However, the high morbidity and mortality rates up to 28% and 9% respectively restrict the use of ALPPS to fit patients under the age of 60 years [130]. The second stage of ALPPS should probably be (temporarily) abolished in patients who develop major complications after the first stage [131].

Although ALPPS is currently performed in all liver backgrounds, histological changes comprising fibrosis, steatosis, and chemotherapy-related alterations resulted in lower hypertrophy rates [130]. The ALPPS procedure resulted in a quadrupled mortality rate, doubled median hospital stay, and doubled risk for PLF in patients with intermediate-stage HCC [132] and should therefore only be

applied in HCC patients with low-grade fibrosis. ALPPS should not, or with great caution, be applied in patients with perihilar and intrahepatic CCA due to the (already) high postoperative mortality rate in this patient category [130,133]. Modifications such as monosegment ALPPS, in which only one instead of two or more Couinaud segments remain, showed promising results in a small cohort of 12 patients, with a PLF rate of 33% but without mortality [134].

*Limiting hepatic haemodynamic imbalance*

Splenectomy and splenic artery ligation can be effective strategies that limit the postresectional increase in portal blood flow and pressure, by activating the hepatic arterial buffer response. These procedures resulted in increased arterial inflow, and enhanced liver regeneration and liver function after (extended) partial hepatectomy in rodent models [135]. Furthermore, in animal models of partial hepatectomy and small-for-size liver grafts, the administration of terlipressin and somatostatin seemed to reduce postresectional portal hyperperfusion and increase regenerative parameters [136–138].

*Providing optimal perioperative care*

Excessive perioperative blood loss, blood transfusion, ischemia-reperfusion injury, and hepatic manipulation predispose to PLF. Blood transfusion enhances postoperative morbidity and tumour recurrence presumably via a transfusion-related inflammatory response [139]. A recent meta-analysis confirmed that hepatic preconditioning (i.e., intermittent vascular inflow occlusion) results in less intraoperative blood loss and a shorter operating time in comparison to hepatectomy alone, but without improved postoperative outcome [140]. Prolonged clamping should nonetheless be avoided since ischemia-reperfusion injury has been shown to induce severe hepatic damage [141]. Hepatic manipulation *per se* elicits an inflammatory response [142]. Methods to minimize mobilisation of the liver include laparoscopic surgery and the hanging method [143]. Laparoscopic resection of HCCs reduced the incidence of PLF compared to open surgery [144].

Since infectious complications such as bile leakage or abdominal collections may contribute to the development of PLF and negatively affect the postresectional course, several preventive measures have been explored. Postresectional primary placement of abdominal drains proved not to be beneficial after major liver resection and is even associated with increased rates of complications such as bile leakage and PLF [145,146]. Multiple human studies focused on either pre- or postresectional antibiotic prophylaxis, without evidence for a significant effect on the rate of infectious complications [147,148]. Preoperative selective bowel contamination has been explored in rodent models, showing amelioration of parenchymal injury and increased liver regeneration after partial liver resection [149]. A meta-analysis of human transplant studies however showed no benefits on infectious complications [150].

*Regenerative interventions*

Augmentation of the regenerative response after liver resection may be an option for prevention and treatment of PLF. The nuclear bile salt receptor FXR (farnesoid X receptor, Fig. 4) may be an attractive therapeutic candidate, through effects on hepatic haemodynamics, bile salt and lipid homeostasis, hepatic inflammation, and hepatocellular proliferation [18,151–153]. Being the key regulator of hepatic bile salt homeostasis, genetic disruption of *Fxr* in mice resulted in mortality and delayed liver regeneration after partial hepatectomy. Conversely, activation of Fxr by its endogenous ligands (i.e., bile salts) or synthetic agonists enhanced liver regeneration in hepatectomized mice. Furthermore, the FXR-regulated enterokine FGF19 reduced mortality

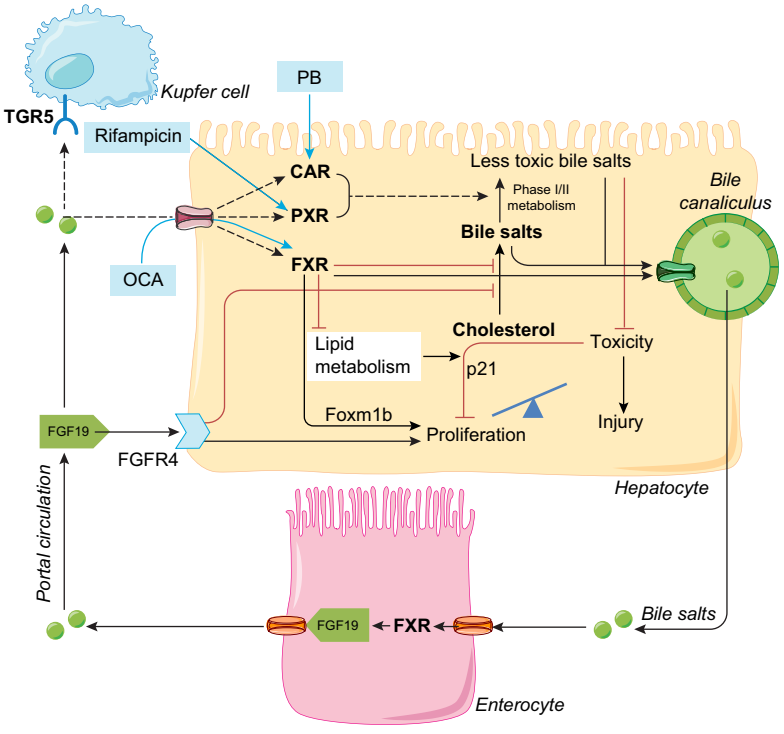


**Fig. 4. Targeting of bile salt receptors may improve liver regeneration after partial hepatectomy through direct trophic and bile salt homeostatic effects.** Control of bile salt homeostasis ensures proper progression of postresectional liver regeneration. Bile salt receptor FXR in small intestine and liver exerts homeostatic control by regulating import, synthesis, conjugation (i.e., *N*-amidation) and export of bile salts. Moreover, bile salt signaling via FXR results in induction of genes engaged in cell cycle control (e.g., *Foxm1b*). On the other hand, hepatic bile salt overload gives rise to liver injury. Bile salt toxicity may be reduced by stimulation of phase I/II metabolism and phase III efflux via agonistic activation of nuclear receptors PXR and CAR. An excessive inflammatory response of Kupffer cells may be dampened by TGR5 agonism. OCA, obeticholic acid (FXR agonist); PB, phenobarbital (CAR activator); FGFR4, fibroblast growth factor receptor 4.

Review

**Key point**

Management of PLF consists of goal-directed therapy and functional support.

in an acute liver failure mouse model [17]. FXR agonists undergo current clinical evaluation, and already showed efficacy in halting fibrotic progression in NASH patients [154].

Bearing in mind that tight control of bile salt homeostasis and hepatic inflammatory tone is warranted to allow normal progression of liver regeneration, targeting of the membrane bile salt receptor TGR5 may be considered in PLF. In the liver, TGR5 is expressed in liver endothelial cells, cholangiocytes, and Kupffer cells [155,156]. Tgr5 enhances bile salt elimination in urine, reduces bile salt hydrophobicity and prevents excessive cytokine production by Kupffer cells, in case of bile salt overload [14]. Other nuclear receptors that play a direct role in liver regeneration, and have the potential to reduce intrahepatic bile salt toxicity by promoting phase I/II metabolism, are the pregnane X receptor and constitutive androstane receptor [157,158]. A recent study showed that the pregnane X receptor agonist rifampicin improved hyperbilirubinemia and clinical status in patients with persistent hepatocellular failure, including one patient with PLF [159]. Despite in-depth knowledge of the processes controlled by the above (nuclear) receptors, their roles in liver regeneration and implication in PLF have only been studied in animal models.

A recently discovered negative regulator of liver regeneration after partial hepatectomy, *viz.* thrombospondin-1 [160], might be a target to accelerate regeneration by antagonizing its action through administration of leucine-serine-lysine-leucine (LSKL) peptide [161]. Likewise, usefulness of colony stimulating factor to accelerate postresectional restoration of phagocytic capacity in the human setting is worth exploring [162]. Given the multifactorial origin of PLF strategies that simultaneously target multiple aetiological pillars may prove most effective.

Transplantation of hepatocytes and other cell types have been moderately successful in several liver diseases in terms of spontaneous recovery or bridging to orthotopic liver transplantation (see reference [163] for a review), and might be of interest for preoperative optimization of liver parenchyma or management of PLF. Moreover, intrahepatic or extrahepatic (scaffold-bound) introduction of induced pluripotent stem cells (iPSC), iPSC-derived or Lgr5$^{+}$ stem cell-derived organoids, cultured hepatocytes are extensively studied in a pre-clinical setting, and might offer advanced possibilities for pre- or postoperative liver repopulation [164–168].

## Management of postoperative liver failure

Due to the lack of randomized controlled trials with PLF as primary outcome measure, almost no treatments for acute and acute-on-chronic liver failure have been validated for PLF. When PLF is detected after resection in (non-)compromised liver, goal-directed therapy and functional support can be offered (Fig. 2).

### *Goal-directed therapy*

PLF is frequently accompanied by multi-organ dysfunction, requiring a systemic treatment approach [169]. Goal-directed therapy focuses on support of circulatory, ventilatory, and renal function in combination with treatment of hepatic encephalopathy, coagulopathy and malnutrition as reviewed elsewhere [1].

### *Functional support*

Molecular absorbent recirculation system, an extracorporeal artificial liver support device that reduces liver failure-induced toxicity by facilitating exchange of albumin-bound and water-soluble toxins from plasma, is applicable as treatment for PLF [170]. In addition, extracorporeal bio-artificial liver devices fulfil functions of the liver (including synthetic and immunological) by separation and passage of blood plasma through a reactor containing layers of animal or human hepatocytes [171]. The recently developed University College London-Liver Dialysis Device extracts albumin by hemofiltration and removes certain endotoxins by haemoperfusion, in combination with human albumin infusion [172]. Unfortunately, although the latter two devices show survival benefits, they have thus far been tested only in a pre-clinical setting. Furthermore, promising treatment modalities that focus on extracorporeal high-flux haemodialysis in combination with albumin dialysis (Prometheus®), and patient plasma replacement with fresh frozen plasma (high-volume plasmapheresis), have been tested almost exclusively as treatment for acute and acute-on-chronic liver failure with sparse (underpowered) data on its use in the context of liver failure after hepatic resection [173,174].

### *Rescue and elective liver transplantation*

The limited data on rescue liver transplantation in patients with PLF showed a 5-year overall survival of 40% [175], however appropriate criteria for patient selection are lacking. Hence, rescue liver transplantation is barely applied nowadays. Moreover, rescue liver transplantation should not be performed if the patient was not eligible for transplantation before partial hepatectomy.

## Conclusion

The incidence of liver failure after surgical resection is relatively low. This is accomplished to a large

extent by (I) better insight into the aetiology of PLF and liver regeneration, (II) new imaging techniques and biochemical tests for preoperative assessment of liver quality, (III) highly effective preventive measures, and (IV) improved perioperative care. Due to the low event rate, prospective studies with PLF as primary endpoint are nearly unachievable [176], and most evidence is based on retrospective cohort studies. Furthermore, a uniform definition and outcome set are lacking, but imperative to compare different cohorts [177]. In view of the current increase of extensive resections in a compromised liver background, the development of universal prediction models, more advanced surgical techniques, and efficient preventive measures become particularly important to obtain curability in these challenging patients. Global collaborations and registrations such as seen in the EASL-CLIF consortium (acute-on-chronic liver failure) [130] or the ALPPS-registry [178] seem the only manner to obtain the required number of events for robust evidence on risk factors, prediction models and interventions.

## Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

## Authors' contributions

Study concept and design: KvM, FS, CD, SOD; Drafting of the manuscript: KvM, Critical revision of the manuscript: FS, CD, SOD; Acquisition of data/Analysis and interpretation of data/Statistical analysis/administrative support/study supervision: n/a. All authors approve of and take responsibility for the final version of this manuscript.

## References

*Author names in bold designate shared co-first authorship*


[1] van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int 2008;28:767–780.

[2] Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ, Edinburgh Liver S, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289–296.

[3] Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824–828, [Discussion 828–829].

[4] Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854–862, [Discussion 862–854].

[5] Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713–724.

[6] Fausto N, Campbell JS, Riehle KJ. Liver regeneration. J Hepatol 2012;57:692–694.

[7] Michalopoulos GK. Principles of liver regeneration and growth homeostasis. Compr Physiol 2013;3:485–513.

[8] Vauthey JN, Abbott DE. Commentary on "Feasibility study of two-stage hepatectomy for bilobar liver metastases". Am J Surg 2012;203:698–699.

[9] Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World J Gastroenterol 2010;16:6046–6057.

[10] Allard MA, Adam R, Bucur PO, Termos S, Cunha AS, Bismuth H, et al. Posthepatectomy portal vein pressure predicts liver failure and mortality after major liver resection on noncirrhotic liver. Ann Surg 2013;258:822–829, [Discussion 829–830].

[11] Golriz M, Majlesara A, El Sakka S, Ashrafi M, Arwin J, Fard N, et al. Small for Size and Flow (SFSF) syndrome: an alternative description for posthepatectomy liver failure. Clin Res Hepatol Gastroenterol 2016;40:267–275.

[12] Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology 2014;146:1625–1638.

[13] **Doignon I**, **Julien B**, Serriere-Lanneau V, Garcin I, Alonso G, Nicou A, et al. Immediate neuroendocrine signaling after partial hepatectomy through acute portal hyperpressure and cholestasis. J Hepatol 2011;54:481–488.

[14] Pean N, Doignon I, Garcin I, Besnard A, Julien B, Liu B, et al. The receptor TGR5 protects the liver from bile acid overload during liver regeneration in mice. Hepatology 2013;58:1451–1460.

[15] Huang W, Ma K, Zhang J, Qatanani M, Cuvillier J, Liu J, et al. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. Science 2006;312:233–236.

[16] Perez MJ, Briz O. Bile-acid-induced cell injury and protection. World J Gastroenterol 2009;15:1677–1689.

[17] Uriarte I, Fernandez-Barrena MG, Monte MJ, Latasa MU, Chang HC, Carotti S, et al. Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice. Gut 2013;62:899–910.

[18] Fan M, Wang X, Xu G, Yan Q, Huang W. Bile acid signaling and liver regeneration. Biochim Biophys Acta 2015;1849:196–200.

[19] Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43:S45–S53.

[20] Chen Y, Sun R. Toll-like receptors in acute liver injury and regeneration. Int Immunopharmacol 2011;11:1433–1441.

[21] Takeishi T, Hirano K, Kobayashi T, Hasegawa G, Hatakeyama K, Naito M. The role of Kupffer cells in liver regeneration. Arch Histol Cytol 1999;62:413–422.

[22] Prins HA, Meijer C, Boelens PG, Diks J, Holtz R, Masson S, et al. Kupffer cell-depleted rats have a diminished acute-phase response following major liver resection. Shock 2004;21:561–565.

[23] Schindl MJ, Millar AM, Redhead DN, Fearon KC, Ross JA, Dejong CH, et al. The adaptive response of the reticuloendothelial system to major liver resection in humans. Ann Surg 2006;243:507–514.

[24] Liu HX, Keane R, Sheng L, Wan YJ. Implications of microbiota and bile acid in liver injury and regeneration. J Hepatol 2015;63:1502–1510.

[25] Liu HX, Rocha CS, Dandekar S, Yvonne Wan YJ. Functional analysis of the relationship between intestinal microbiota and the expression of hepatic genes and pathways during the course of liver regeneration. J Hepatol 2016;64:641–650.

[26] Joyce SA, MacSharry J, Casey PG, Kinsella M, Murphy EF, Shanahan F, et al. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. Proc Natl Acad Sci U S A 2014;111:7421–7426.

[27] Sayin SI, Wahlstrom A, Felin J, Jantti S, Marschall HU, Bamberg K, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab 2013;17:225–235.

[28] Liu HX, Hu Y, Wan YY. Microbiota and bile acid profiles in retinoic acid-primed mice that exhibit accelerated liver regeneration. Oncotarget 2016;7:1096–1106.

[29] Cornell RP. Gut-derived endotoxin elicits hepatotrophic factor secretion for liver regeneration. Am J Physiol 1985;249:R551–R562.

[30] Cornell RP. Restriction of gut-derived endotoxin impairs DNA synthesis for liver regeneration. Am J Physiol 1985;249:R563–R569.

[31] Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-

based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460–466.
[32] Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008;247:118–124.
[33] Soubrane O, Brouquet A, Zalinski S, Terris B, Brezault C, Mallet V, et al. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg 2010;251:454–460.
[34] Vigano L, Ravarino N, Ferrero A, Motta M, Torchio B, Capussotti L. Prospective evaluation of accuracy of liver biopsy findings in the identification of chemotherapy-associated liver injuries. Arch Surg 2012;147:1085–1091.
[35] Schiffer E, Frossard JL, Rubbia-Brandt L, Mentha G, Pastor CM. Hepatic regeneration is decreased in a rat model of sinusoidal obstruction syndrome. J Surg Oncol 2009;99:439–446.
[36] Hubert C, Dahrenmoller C, Marique L, Jabbour N, Gianello P, Leclercq I. Hepatic regeneration in a rat model is impaired by chemotherapy agents used in metastatic colorectal cancer. Eur J Surg Oncol 2015;41:1471–1478.
[37] Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007;110:2761–2767.
[38] Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology 2010;56:430–439.
[39] Imai K, Emi Y, Iyama KI, Beppu T, Ogata Y, Kakeji Y, et al. Splenic volume may be a useful indicator of the protective effect of bevacizumab against oxaliplatin-induced hepatic sinusoidal obstruction syndrome. Eur J Surg Oncol 2014;40:559–566.
[40] Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010;28:2549–2555.
[41] Ward J, Guthrie JA, Sheridan MB, Boyes S, Smith JT, Wilson D, et al. Sinusoidal obstructive syndrome diagnosed with superparamagnetic iron oxide-enhanced magnetic resonance imaging in patients with chemotherapy-treated colorectal liver metastases. J Clin Oncol 2008;26:4304–4310.
[42] Shin NY, Kim MJ, Lim JS, Park MS, Chung YE, Choi JY, et al. Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. Eur Radiol 2012;22:864–871.
[43] Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990;11:787–797.
[44] Vigano L, Rubbia-Brandt L, De Rosa G, Majno P, Langella S, Toso C, et al. Nodular regenerative hyperplasia in patients undergoing liver resection for colorectal metastases after chemotherapy: risk factors, preoperative assessment and clinical impact. Ann Surg Oncol 2015;22:4149–4157.
[45] van den Broek MA, Olde Damink SW, Driessen A, Dejong CH, Bemelmans MH. Nodular regenerative hyperplasia secondary to neoadjuvant chemotherapy for colorectal liver metastases. Case Rep Med 2009;2009:457975.
[46] Wicherts DA, de Haas RJ, Sebagh M, Ciacio O, Levi F, Paule B, et al. Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases. Ann Surg Oncol 2011;18:659–669.
[47] Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:4287–4299.
[48] Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065–2072.
[49] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.
[50] Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg 2002;6:88–94.
[51] Newberry EP, Kennedy SM, Xie Y, Luo J, Stanley SE, Semenkovich CF, et al. Altered hepatic triglyceride content after partial hepatectomy without impaired liver regeneration in multiple murine genetic models. Hepatology 2008;48:1097–1105.
[52] de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg 2010;97:1331–1339.
[53] Reddy SK, Marsh JW, Varley PR, Mock BK, Chopra KB, Geller DA, et al. Underlying steatohepatitis, but not simple hepatic steatosis, increases morbidity after liver resection: a case-control study. Hepatology 2012;56:2221–2230.
[54] Tashiro H, Kuroda S, Mikuriya Y, Ohdan H. Ischemia-reperfusion injury in patients with fatty liver and the clinical impact of steatotic liver on hepatic surgery. Surg Today 2014;44:1611–1625.
[55] Vetelainen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. Ann Surg 2007;245:20–30.
[56] Selzner M, Clavien PA. Failure of regeneration of the steatotic rat liver: disruption at two different levels in the regeneration pathway. Hepatology 2000;31:35–42.
[57] Yang SQ, Lin HZ, Mandal AK, Huang J, Diehl AM. Disrupted signaling and inhibited regeneration in obese mice with fatty livers: implications for nonalcoholic fatty liver disease pathophysiology. Hepatology 2001;34:694–706.
[58] Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. Liver Int 2008;28:705–712.
[59] Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614–2618.
[60] de Moura Almeida A, Cotrim HP, Barbosa DB, de Athayde LG, Santos AS, Bitencourt AG, et al. Fatty liver disease in severe obese patients: diagnostic value of abdominal ultrasound. World J Gastroenterol 2008;14:1415–1418.
[61] Lee SS, Park SH, Kim HJ, Kim SY, Kim MY, Kim DY, et al. Non-invasive assessment of hepatic steatosis: prospective comparison of the accuracy of imaging examinations. J Hepatol 2010;52:579–585.
[62] Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011;54:650–659.
[63] Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology 2014;60:1920–1928.
[64] de Ledinghen V, Vergniol J, Foucher J, El-Hajbi F, Merrouche W, Rigalleau V. Feasibility of liver transient elastography with FibroScan using a new probe for obese patients. Liver Int 2010;30:1043–1048.
[65] Shi KQ, Tang JZ, Zhu XL, Ying L, Li DW, Gao J, et al. Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. J Gastroenterol Hepatol 2014;29:1149–1158.
[66] Palmeri ML, Wang MH, Rouze NC, Abdelmalek MF, Guy CD, Moser B, et al. Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease. J Hepatol 2011;55:666–672.
[67] Shen J, Chan HL, Wong GL, Choi PC, Chan AW, Chan HY, et al. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. J Hepatol 2012;56:1363–1370.
[68] Cusi K, Chang Z, Harrison S, Lomonaco R, Bril F, Orsak B, et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol 2014;60:167–174.
[69] Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol 2012;12:2.
[70] Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008;57:1441–1447.
[71] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–854.
[72] Cales P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konate A, et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology 2005;42:1373–1381.
[73] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–526.
[74] de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol 2012;56:S75–S87.

[75] Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. Liver Transpl 2004;10:S46–S52.
[76] Kuramitsu K, Sverdlov DY, Liu SB, Csizmadia E, Burkly L, Schuppan D, et al. Failure of fibrotic liver regeneration in mice is linked to a severe fibrogenic response driven by hepatic progenitor cell activation. Am J Pathol 2013;183:182–194.
[77] Kato A, Bamba H, Shinohara M, Yamauchi A, Ota S, Kawamoto C, et al. Relationship between expression of cyclin D1 and impaired liver regeneration observed in fibrotic or cirrhotic rats. J Gastroenterol Hepatol 2005;20:1198–1205.
[78] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–1324.
[79] Vibhakorn S, Cholongitas E, Kalambokis G, Manousou P, Quaglia A, Marelli L, et al. A comparison of four- *vs.* three-pass transjugular biopsy using a 19-G Tru-Cut needle and a randomized study using a cassette to prevent biopsy fragmentation. Cardiovasc Intervent Radiol 2009;32:508–513.
[80] Wong GL, Espinosa WZ, Wong VW. Personalized management of cirrhosis by non-invasive tests of liver fibrosis. Clin Mol Hepatol 2015;21:200–211.
[81] Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, et al. Meta-analysis: ARFI elastography *vs.* transient elastography for the evaluation of liver fibrosis. Liver Int 2013;33:1138–1147.
[82] Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749–1761.
[83] Verloh N, Utpatel K, Haimerl M, Zeman F, Fellner C, Fichtner-Feigl S, et al. Liver fibrosis and Gd-EOB-DTPA-enhanced MRI: a histopathologic correlation. Sci Rep 2015;5:15408.
[84] Lin XJ, Yang J, Chen XB, Zhang M, Xu MQ. The critical value of remnant liver volume-to-body weight ratio to estimate posthepatectomy liver failure in cirrhotic patients. J Surg Res 2014;188:489–495.
[85] Chen X, Zhai J, Cai X, Zhang Y, Wei L, Shi L, et al. Severity of portal hypertension and prediction of postoperative liver failure after liver resection in patients with Child-Pugh grade A cirrhosis. Br J Surg 2012;99:1701–1710.
[86] Cucchetti A, Cescon M, Golfieri R, Piscaglia F, Renzulli M, Neri F, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. J Hepatol 2016;64:79–86.
[87] Desmet VJ. Histopathology of cholestasis. Verh Dtsch Ges Pathol 1995;79:233–240.
[88] Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. Clin Gastroenterol Hepatol 2013;11:13–21, [Quiz e13–e14] e11.
[89] Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol 2012;19:1602–1608.
[90] Nuzzo G, Giuliante F, Ardito F, Giovannini I, Aldrighetti L, Belli G, et al. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients. Arch Surg 2012;147:26–34.
[91] **Wiggers JK**, **Koerkamp BG**, Cieslak KP, Doussot A, van Klaveren D, Allen PJ, et al. Postoperative mortality after liver resection for perihilar cholangiocarcinoma: development of a risk score and importance of biliary drainage of the future liver remnant. J Am Coll Surg 2016;223:321–331.e1.
[92] Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84–96.
[93] Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. J Hepatobiliary Pancreat Surg 2007;14:159–166.
[94] Tracy Jr TF, Bailey PV, Goerke ME, Sotelo-Avila C, Weber TR. Cholestasis without cirrhosis alters regulatory liver gene expression and inhibits hepatic regeneration. Surgery 1991;110:176–182, [Discussion 182–173].
[95] Yoshidome H, Miyazaki M, Shimizu H, Ito H, Nakagawa K, Ambiru S, et al. Obstructive jaundice impairs hepatic sinusoidal endothelial cell function and renders liver susceptible to hepatic ischemia/reperfusion. J Hepatol 2000;33:59–67.
[96] Gehring S, Dickson EM, San Martin ME, van Rooijen N, Papa EF, Harty MW, et al. Kupffer cells abrogate cholestatic liver injury in mice. Gastroenterology 2006;130:810–822.
[97] Morita Y, Yoshidome H, Kimura F, Shimizu H, Ohtsuka M, Takeuchi D, et al. Excessive inflammation but decreased immunological response renders liver susceptible to infection in bile duct ligated mice. J Surg Res 2008;146:262–270.
[98] Kuzu MA, Kale IT, Col C, Tekeli A, Tanik A, Koksoy C. Obstructive jaundice promotes bacterial translocation in humans. Hepatogastroenterology 1999;46:2159–2164.
[99] Liver EAftSot. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–267.
[100] Mosler P. Diagnosis and management of acute cholangitis. Curr Gastroenterol Rep 2011;13:166–172.
[101] **van der Vorst JR**, **van Dam RM**, van Stiphout RS, van den Broek MA, Hollander IH, Kessels AG, et al. Virtual liver resection and volumetric analysis of the future liver remnant using open source image processing software. World J Surg 2010;34:2426–2433.
[102] **Dello SA**, **van Dam RM**, Slangen JJ, van de Poll MC, Bemelmans MH, Greve JW, et al. Liver volumetry plug and play: do it yourself with ImageJ. World J Surg 2007;31:2215–2221.
[103] **Mao Y**, **Du S**, **Ba J**, Li F, Yang H, Lu X, et al. Using Dynamic 99mT c-GSA SPECT/CT fusion images for hepatectomy planning and postoperative liver failure prediction. Ann Surg Oncol 2015;22:1301–1307.
[104] Verloh N, Haimerl M, Zeman F, Schlabeck M, Barreiros A, Loss M, et al. Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. Eur Radiol 2014;24:1013–1019.
[105] de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ. (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. J Nucl Med 2010;51:229–236.
[106] Robinson SM, Mann J, Vasilaki A, Mathers J, Burt AD, Oakley F, et al. Pathogenesis of FOLFOX induced sinusoidal obstruction syndrome in a murine chemotherapy model. J Hepatol 2013;59:318–326.
[107] Benimetskaya L, Wu S, Voskresenskiy AM, Echart C, Zhou JF, Shin J, et al. Angiogenesis alteration by defibrotide: implications for its mechanism of action in severe hepatic veno-occlusive disease. Blood 2008;112:4343–4352.
[108] Brouquet A, Benoist S, Julie C, Penna C, Beauchet A, Rougier P, et al. Risk factors for chemotherapy-associated liver injuries: a multivariate analysis of a group of 146 patients with colorectal metastases. Surgery 2009;145:362–371.
[109] Ezzat T, van den Broek MA, Davies N, Dejong CH, Bast A, Malago M, et al. The flavonoid monoHER prevents monocrotaline-induced hepatic sinusoidal injury in rats. J Surg Oncol 2012;106:72–78.
[110] Schwarz L, Faitot F, Soubrane O, Scatton O. Splenic artery ligation for severe oxaliplatin induced portal hypertension: a way to improve postoperative course and allow adjuvant chemotherapy for colorectal liver metastases: Letter to editor: comment about "Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases". Eur J Surg Oncol 2014;40:787–788.
[111] Doyle A, Dillon J, MacArthur M, Marquez M, Smith R, Grant D, et al. Treatment with optifast reduces hepatic steatosis and safely increases candidacy rates for live donor liver transplantation. The AASLD Liver Meeting, 2015.
[112] Reeves JG, Suriawinata AA, Ng DP, Holubar SD, Mills JB, Barth Jr RJ. Short-term preoperative diet modification reduces steatosis and blood loss in patients undergoing liver resection. Surgery 2013;154:1031–1037.
[113] Giannini E, Borro P, Botta F, Fumagalli A, Malfatti F, Podesta E, et al. Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. J Hepatol 2002;37:572–577.
[114] Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. Ann Surg 2011;253:759–763.
[115] van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362:129–137.
[116] Farges O, Regimbeau JM, Fuks D, Le Treut YP, Cherqui D, Bachellier P, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg 2013;100:274–283.
[117] Ferrero A, Lo Tesoriere R, Vigano L, Caggiano L, Sgotto E, Capussotti L. Preoperative biliary drainage increases infectious complications after hepatectomy for proximal bile duct tumor obstruction. World J Surg 2009;33:318–325.
[118] Hochwald SN, Burke EC, Jarnagin WR, Fong Y, Blumgart LH. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. Arch Surg 1999;134:261–266.
[119] Kloek JJ, van der Gaag NA, Aziz Y, Rauws EA, van Delden OM, Lameris JS, et al. Endoscopic and percutaneous preoperative biliary drainage in patients with suspected hilar cholangiocarcinoma. J Gastrointest Surg 2010;14:119–125.
[120] Ishizawa T, Hasegawa K, Sano K, Imamura H, Kokudo N, Makuuchi M. Selective *vs.* total biliary drainage for obstructive jaundice caused by a hepatobiliary malignancy. Am J Surg 2007;193:149–154.
[121] van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol 2013;36:25–34.

[122] Pandanaboyana S, Bell R, Hidalgo E, Toogood G, Prasad KR, Bartlett A, et al. A systematic review and meta-analysis of portal vein ligation *vs.* portal vein embolization for elective liver resection. Surgery 2015;157:690–698.

[123] **Malinowski M**, **Geisel D**, Stary V, Denecke T, Seehofer D, Jara M, et al. Portal vein embolization with plug/coils improves hepatectomy outcome. J Surg Res 2015;194:202–211.

[124] Hoekstra LT, van Lienden KP, Doets A, Busch OR, Gouma DJ, van Gulik TM. Tumor progression after preoperative portal vein embolization. Ann Surg 2012;256:812–817, [Discussion 817–818].

[125] Vetelainen R, van Vliet AK, van Gulik TM. Severe steatosis increases hepatocellular injury and impairs liver regeneration in a rat model of partial hepatectomy. Ann Surg 2007;245:44–50.

[126] Narita M, Oussoultzoglou E, Chenard MP, Rosso E, Casnedi S, Pessaux P, et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surg Today 2011;41:7–17.

[127] de Baere T, Teriitehau C, Deschamps F, Catherine L, Rao P, Hakime A, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. Ann Surg Oncol 2010;17:2081–2089.

[128] Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208–217.

[129] **Schnitzbauer AA**, **Lang SA**, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405–414.

[130] Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260:829–836, [Discussion 836–828].

[131] Truant S, Scatton O, Dokmak S, Regimbeau JM, Lucidi V, Laurent A, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. Eur J Surg Oncol 2015;41:674–682.

[132] D'Haese JG, Neumann J, Weniger M, Pratschke S, Bjornsson B, Ardiles V, et al. Should ALPPS be used for liver resection in intermediate-stage HCC? Ann Surg Oncol 2016;23:1335–1343.

[133] Serenari M, Zanello M, Schadde E, Toschi E, Ratti F, Gringeri E, et al. Importance of primary indication and liver function between stages: results of a multicenter Italian audit of ALPPS 2012–2014. HPB 2016;18:419–427.

[134] **Schadde E**, **Malago M**, Hernandez-Alejandro R, Li J, Abdalla E, Ardiles V, et al. Monosegment ALPPS hepatectomy: extending resectability by rapid hypertrophy. Surgery 2015;157:676–689.

[135] **Ren YS**, **Qian NS**, Tang Y, Liao YH, Liu WH, Raut V, et al. Beneficial effects of splenectomy on liver regeneration in a rat model of massive hepatectomy. Hepatobiliary Pancreat Dis Int 2012;11:60–65.

[136] Ren Z, Xu Y, Zhu S. The effect of terlipressin on hepatic hemodynamics in small-for-size livers. Hepatogastroenterology 2012;59:208–211.

[137] Fahrner R, Patsenker E, de Gottardi A, Stickel F, Montani M, Stroka D, et al. Elevated liver regeneration in response to pharmacological reduction of elevated portal venous pressure by terlipressin after partial hepatectomy. Transplantation 2014;97:892–900.

[138] Xu X, Man K, Zheng SS, Liang TB, Lee TK, Ng KT, et al. Attenuation of acute phase shear stress by somatostatin improves small-for-size liver graft survival. Liver Transpl 2006;12:621–627.

[139] Miki C, Hiro J, Ojima E, Inoue Y, Mohri Y, Kusunoki M. Perioperative allogeneic blood transfusion, the related cytokine response and long-term survival after potentially curative resection of colorectal cancer. Clin Oncol (R Coll Radiol) 2006;18:60–66.

[140] Simillis C, Robertson FP, Afxentiou T, Davidson BR, Gurusamy KS. A network metaanalysis comparing perioperative outcomes of interventions aiming to decrease ischemia reperfusion injury during elective liver resection. Surgery 2016;159:1157–1169.

[141] Datta G, Fuller BJ, Davidson BR. Molecular mechanisms of liver ischemia reperfusion injury: insights from transgenic knockout models. World J Gastroenterol 2013;19:1683–1698.

[142] van den Broek MA, Shiri-Sverdlov R, Schreurs JJ, Bloemen JG, Bieghs V, Rensen SS, et al. Liver manipulation during liver surgery in humans is associated with hepatocellular damage and hepatic inflammation. Liver Int 2013;33:633–641.

[143] Belghiti J, Guevara OA, Noun R, Saldinger PF, Kianmanesh R. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. J Am Coll Surg 2001;193:109–111.

[144] Morise Z, Ciria R, Cherqui D, Chen KH, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 2015;22:342–352.

[145] Squires 3rd MH, Lad NL, Fisher SB, Kooby DA, Weber SM, Brinkman A, et al. Value of primary operative drain placement after major hepatectomy: a multi-institutional analysis of 1,041 patients. J Am Coll Surg 2015;220:396–402.

[146] **Olthof PB**, **Coelen RJ**, Wiggers JK, Besselink MG, Busch OR, van Gulik TM. External biliary drainage following major liver resection for perihilar cholangiocarcinoma: impact on development of liver failure and biliary leakage. HPB 2016;18:348–353.

[147] Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al. Evaluation of postoperative antibiotic prophylaxis after liver resection: a randomized controlled trial. Am J Surg 2013;206:8–15.

[148] **Zhou YM**, **Chen ZY**, Li XD, Xu DH, Su X, Li B. Preoperative antibiotic prophylaxis does not reduce the risk of postoperative infectious complications in patients undergoing elective hepatectomy. Dig Dis Sci 2016;61:1707–1713.

[149] Ren W, Wang X, Zhang A, Li C, Chen G, Ge X, et al. Selective bowel decontamination improves the survival of 90% hepatectomy in rats. J Surg Res 2015;195:454–464.

[150] Gurusamy KS, Nagendran M, Davidson BR. Methods of preventing bacterial sepsis and wound complications after liver transplantation. Cochrane Database Syst Rev 2014:CD006660.

[151] Verbeke L, Farre R, Trebicka J, Komuta M, Roskams T, Klein S, et al. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats. Hepatology 2014;59:2286–2298.

[152] Hollman DA, Milona A, van Erpecum KJ, van Mil SW. Anti-inflammatory and metabolic actions of FXR: insights into molecular mechanisms. Biochim Biophys Acta 2012;1821:1443–1452.

[153] Schaap FG, Trauner M, Jansen PL. Bile acid receptors as targets for drug development. Nat Rev Gastroenterol Hepatol 2014;11:55–67.

[154] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956–965.

[155] Keitel V, Donner M, Winandy S, Kubitz R, Haussinger D. Expression and function of the bile acid receptor TGR5 in Kupffer cells. Biochem Biophys Res Commun 2008;372:78–84.

[156] Keitel V, Haussinger D. TGR5 in the biliary tree. Dig Dis 2011;29:45–47.

[157] Wagner M, Halilbasic E, Marschall HU, Zollner G, Fickert P, Langner C, et al. CAR and PXR agonists stimulate hepatic bile acid and bilirubin detoxification and elimination pathways in mice. Hepatology 2005;42:420–430.

[158] Tschuor C, Kachaylo E, Limani P, Raptis DA, Linecker M, Tian Y, et al. Constitutive androstane receptor (Car)-driven regeneration protects liver from failure following tissue loss. J Hepatol 2016;65:66–74.

[159] van Dijk R, Kremer AE, Smit W, van den Elzen B, van Gulik T, Gouma D, et al. Characterization and treatment of persistent hepatocellular secretory failure. Liver Int 2015;35:1478–1488.

[160] Hayashi H, Sakai K, Baba H, Sakai T. Thrombospondin-1 is a novel negative regulator of liver regeneration after partial hepatectomy through transforming growth factor-beta1 activation in mice. Hepatology 2012;55:1562–1573.

[161] Kuroki H, Hayashi H, Nakagawa S, Sakamoto K, Higashi T, Nitta H, et al. Effect of LSKL peptide on thrombospondin 1-mediated transforming growth factor beta signal activation and liver regeneration after hepatectomy in an experimental model. Br J Surg 2015;102:813–825.

[162] Stutchfield BM, Antoine DJ, Mackinnon AC, Gow DJ, Bain CC, Hawley CA, et al. CSF1 Restores Innate Immunity After Liver Injury in Mice and Serum Levels Indicate Outcomes of Patients With Acute Liver Failure. Gastroenterology 2015;149:1896–1909 e1814.

[163] Forbes SJ, Gupta S, Dhawan A. Cell therapy for liver disease: from liver transplantation to cell factory. J Hepatol 2015;62:S157–S169.

[164] Duncan AW, Dorrell C, Grompe M. Stem cells and liver regeneration. Gastroenterology 2009;137:466–481.

[165] **Huch M**, **Dorrell C**, Boj SF, van Es JH, Li VS, van de Wetering M, et al. In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. Nature 2013;494:247–250.

[166] **Huang P**, **Zhang L**, **Gao Y**, **He Z**, Yao D, Wu Z, et al. Direct reprogramming of human fibroblasts to functional and expandable hepatocytes. Cell Stem Cell 2014;14:370–384.

[167] Takebe T, Sekine K, Enomura M, Koike H, Kimura M, Ogaeri T, et al. Vascularized and functional human liver from an iPSC-derived organ bud transplant. Nature 2013;499:481–484.
[168] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–676.
[169] Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, et al. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. J Surg Res 2006;133:102–112.
[170] van de Kerkhove MP, de Jong KP, Rijken AM, de Pont AC, van Gulik TM. MARS treatment in posthepatectomy liver failure. Liver Int 2003;23:44–51.
[171] van Wenum M, Chamuleau RA, van Gulik TM, Siliakus A, Seppen J, Hoekstra R. Bioartificial livers in vitro and in vivo: tailoring biocomponents to the expanding variety of applications. Expert Opin Biol Ther 2014;14:1745–1760.
[172] Lee KC, Baker LA, Stanzani G, Alibhai H, Chang YM, Jimenez Palacios C, et al. Extracorporeal liver assist device to exchange albumin and remove endotoxin in acute liver failure: results of a pivotal pre-clinical study. J Hepatol 2015;63:634–642.
[173] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 2016;64:69–78.
[174] Rifai K, Ernst T, Kretschmer U, Bahr MJ, Schneider A, Hafer C, et al. Prometheus–a new extracorporeal system for the treatment of liver failure. J Hepatol 2003;39:984–990.
[175] Otsuka Y, Duffy JP, Saab S, Farmer DG, Ghobrial RM, Hiatt JR, et al. Postresection hepatic failure: successful treatment with liver transplantation. Liver transpl 2007;13:672–679.
[176] **van den Broek MA**, **van Dam RM**, Malago M, Dejong CH, van Breukelen GJ, Olde Damink SW. Feasibility of randomized controlled trials in liver surgery using surgery-related mortality or morbidity as endpoint. Br J Surg 2009;96:1005–1014.
[177] van den Broek MA, van Dam RM, van Breukelen GJ, Bemelmans MH, Oussoultzoglou E, Pessaux P, et al. Development of a composite endpoint for randomized controlled trials in liver surgery. Br J Surg 2011;98:1138–1145.
[178] Arroyo V, Moreau R, Jalan R, Gines P. Study E-CCC. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol 2015;62:S131–S143.