OXFORD

BJS Open, 2022, zrac142
https://doi.org/10.1093/bjsopen/zrac142
Review Article

Current evidence on posthepatectomy liver failure: comprehensive review

Ernesto Sparrelid[1,*], Pim B. Olthof[2,3], Bobby V. M. Dasari[4,5], Joris I. Erdmann[3], Jonas Santol[6,7], Patrick Starlinger[8,9] and Stefan Gilg[1]

[1]Department of Clinical Science, Intervention and Technology, Division of Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[2]Department of Surgery, Erasmus MC, Rotterdam, The Netherlands
[3]Department of Surgery, Amsterdam UMC, Amsterdam, The Netherlands
[4]Department of HPB Surgery and Liver Transplantation, Queen Elizabeth Hospital, Birmingham, UK
[5]University of Birmingham, Birmingham, UK
[6]Department of Surgery, HPB Center, Viennese Health Network, Clinic Favoriten and Sigmund Freud Private University, Vienna, Austria
[7]Department of Vascular Biology and Thrombosis Research, Centre of Physiology and Pharmacology, Medical University of Vienna, Vienna, Austria
[8]Division of General Surgery, Department of Surgery, Medical University of Vienna, General Hospital of Vienna, Vienna, Austria
[9]Department of Surgery, Division of Hepatobiliary and Pancreas Surgery, Mayo Clinic, Rochester, New York, USA

Correspondence to: Ernesto Sparrelid, Department of Clinical Science, Intervention and Technology, Division of Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (e-mail: ernesto.sparrelid@ki.se)

Abstract

Introduction: Despite important advances in many areas of hepatobiliary surgical practice during the past decades, posthepatectomy liver failure (PHLF) still represents an important clinical challenge for the hepatobiliary surgeon. The aim of this review is to present the current body of evidence regarding different aspects of PHLF.

Methods: A literature review was conducted to identify relevant articles for each topic of PHLF covered in this review. The literature search was performed using Medical Subject Heading terms on PubMed for articles on PHLF in English until May 2022.

Results: Uniform reporting on PHLF is lacking due to the use of various definitions in the literature. There is no consensus on optimal preoperative assessment before major hepatectomy to avoid PHLF, although many try to estimate future liver remnant function. Once PHLF occurs, there is still no effective treatment, except liver transplantation, where the reported experience is limited.

Discussion: Strict adherence to one definition is advised when reporting data on PHLF. The use of the International Study Group of Liver Surgery criteria of PHLF is recommended. There is still no widespread established method for future liver remnant function assessment. Liver transplantation is currently the only effective way to treat severe, intractable PHLF, but for many indications, this treatment is not available in most countries.

Introduction

Despite important advances in many areas of hepatobiliary surgical practice during the last decades, posthepatectomy liver failure (PHLF) still represents an important clinical challenge for the hepatobiliary surgeon. Even if clinically relevant PHLF is not the most common complication after a liver resection, it continues to be the leading cause for postoperative fatalities even in modern practice at tertiary centres[1,2].

There are several challenges regarding PHLF. First, there are no universal diagnostic criteria for reporting on PHLF in the literature making comparison of published articles difficult. Even with an increased usage of the PHLF criteria presented by the International Study Group of Liver Surgery (ISGLS) in 2011[3], numerous variations still occur in recent publications. Second, accurate preoperative methods for assessing whether the remnant liver after surgery will be sufficient to sustain function in the postoperative regenerative interval are lacking. Third, although liver regeneration has been studied extensively (mostly in animal models) and many pathways have been identified[4,5], there is still no clear way to transfer this knowledge into clinically useful methods. Fourth, once PHLF occurs, we have no effective means to treat this condition despite many different attempts to support the regenerating remnant liver. So, presently the best way to treat PHLF is to avoid it from occurring.

A literature review was conducted to identify relevant articles for each topic of PHLF covered. The literature search was performed using Medical Subject Heading terms on PubMed for articles on PHLF in English until May 2022. A formal systematic literature search according to the PRISMA guidelines[6] was not undertaken.

The aim of this review is to present the current body of evidence regarding several aspects of PHLF, provide insight into the pathophysiology of this condition, which measures can be undertaken before surgery to prevent PHLF from occurring and how to handle the patient if this feared complication still occurs.

Definitions and epidemiology

Definitions and prediction

Since the beginning of the 21st century, a lot of scientific effort has been undertaken to describe, classify, and predict PHLF. In the

Received: July 19, 2022. **Revised:** September 21, 2022. **Accepted:** October 03, 2022

1960s, there was a remarkable amount of knowledge about the physiological effects of major hepatic resections on liver function[7]; however, since that time, liver dysfunction has been described and measured in numerous ways, making it difficult to compare scientific reports in this field. In 2005, Balzan *et al.* published an article in which they were the first to systematically describe clinically relevant liver failure. Based on blood samples (bilirubin and prothrombin time) on postoperative day five, they could predict 60-day fatalities[8]. Another definition was proposed by Mullen *et al.* in 2010, focusing only on peak bilirubin in the postoperative course[9]. The major weakness of these two criteria was their binarity, only comparing PHLF to non-PHLF. To overcome this, the ISGLS developed a new definition based on an expert consensus meeting, providing criteria containing three different grades of PHLF (grade A–C)[3]. The grading is based on bilirubin and prothrombin time on or after postoperative day five and changes in the clinical course of patients undergoing hepatectomy. Presently, the ISGLS PHLF criteria are the most frequently used in literature to define PHLF. Several aspects of the ISGLS criteria have been discussed, such as the potentially lacking clinical relevance of grade A[10,11] and that the criteria do not contain a distinction between primary and secondary liver failure[1]. A major problem of the definitions and predictive models mentioned above is their time point of applicability. On or after postoperative day five, there are limited possibilities left to substantially influence and potentially treat postoperative liver dysfunction, given the immediate onset of liver regeneration after hepatectomy[13]. Recently, perioperative lactate dynamics were found to be suitable for early recognition of PHLF and prediction of both rate and fatalities[14]; however, these attempts have not resulted in new and widely used definitions. Thus, to allow comparability of reported results, many suggest using the ISGLS criteria until a new definition, based on a broad international agreement, is available. New definitions should, however, address an urgent need to develop predictive models and definitions that can be applied in the first 48 h after surgery, to guide possible treatment decisions for these patients. The most used criteria of PHLF are presented in *Table 1*.

Epidemiology

The incidence of PHLF is highly dependent on which definition is used and the reported cohort of patients (for example demographic data, diagnosis, and extent of resection)[15]. Using the ISGLS criteria, the incidence of PHLF in recent publications ranges between 9 per cent[16] and about 20 per cent in western cohorts at tertiary centres[14]; however, in population-based studies, a significant difference in 90-day fatalities following hepatectomy has been reported when comparing low- and high-volume centres[1,17]. As PHLF has been found to be the single most important cause for 90-day fatalities[2] and research regarding PHLF mostly originates from high-volume centres, a different incidence of PHLF in other settings could be possible. For example, in a recent study facilitating data from the National Surgical Quality Improvement Program database in the USA on both minor and major hepatectomies, the incidence of all ISGLS grades of PHLF was under 5 per cent[18].

Several approaches have been undertaken to risk stratify patients before surgery. One PHLF risk score found that simple blood tests and extent of surgery could predict PHLF[19]. The combination of the aspartate aminotransferase/platelet ratio index (APRI) and albumin–bilirubin grade (ALBI) score, demonstrated good preoperative risk assessment of postoperative outcome, both in eastern hepatocellular cancer cohorts[20], as well as in a population-based western setting, including PHLF (ISGLS grade C) and 30-day fatalities[18]. Another interesting approach has been undertaken in a French multicentre study, that developed a risk calculator for PHLF in patients with cirrhosis, considering both pre-, peri-, and postoperative variables[21]. The study tried to reflect the fact that the incidence of PHLF is not only influenced by preoperative factors, but also by peri- and postoperative events. Finally, there are some promising circulating factors in blood that have been assessed as preoperative predictors for

Table 1 Summary of the most important definitions of posthepatectomy liver failure

Definition (original publication)	Description	Predictive value (original publication)	Study population	Validation studies
ISGLS criteria (Rahbari *et al.*[3])	Severity grading (PHLF grade A, B and C) based on clinical and laboratory parameters on or after postoperative day 5	Grade A–C: perioperative (30-day) fatalities OR 13.80; 95% c.i. 4.27–44.61; 99% sensitivity and 91% specificity for detection of fatalities	Definition based on literature review and consensus of ISGLS members. Original publication refers to data from single-centre experience, 835 patients, year 2002–2010, 9% cirrhosis	Calthorpe *et al.*[10] Sultana *et al.*[16] Skrzypczyk *et al.*[219] Rahbari *et al.*[15]
50:50, Balzan criteria (Balzan *et al.*[8])	Bilirubin and PT on postoperative day 5	If bilirubin >50 μmol/l and PT <50% on postoperative day 5: Relative risk of death 66 (95% c.i. 30,147) 59% 60-day fatalities	Single-centre, 775 patients, years 1998–2002, 12% cirrhosis	Calthorpe *et al.*[10] Sultana *et al.*[16] Skrzypczyk *et al.*[219]
Mullen, peak bilirubin criteria (Mullen *et al.*[9])	Postoperative peak serum bilirubin concentration more than 7 mg/dl	Prediction of liver-related death: sensitivity 93%; specificity 94% 90-day mortality (OR 10.8), 90-day liver-related fatalities (OR 250)	Three centres, 1059 non-cirrhotic patients, years 1995–2005	Calthorpe *et al.*[10] Skrzypczyk *et al.*[219] Sultana *et al.*[16]

ISGLS, International Study Group of Liver Surgery; PT, prothrombin time.

PHLF[22,23], but they will require further validation before their clinical use can be established.

It is presently unclear as to what extent these tools have been introduced in general clinical practice and whether some of these predictive methods are widely used for preoperative patient selection. Thus, it still is difficult to accurately predict the incidence and individual risk of patients to develop PHLF before surgery[24]; however, preoperative prediction might help to guide preventive measures and even treatments before hepatectomy in the future.

Aetiology

Basic science, loss of function, and liver regeneration

Modern liver surgery is only made possible by the liver's unique ability to regenerate. While most patients recover rapidly after liver resection, some develop PHLF. In this context, it is important to note that the liver is challenged on multiple levels after hepatic resection. When there is significant liver volume loss, resulting in a significant reduction of available hepatocytes to maintain liver metabolic function (excretory and synthetic), regenerative activity also demands significant energy, ultimately potentially resulting in an 'energy crisis'. Particularly, mitotic activity appears with a trade-off in functional activity[25]. With ongoing liver regeneration, energy levels of the liver slowly recover and allow the return of metabolic function. The higher hepatic tissue loss, the higher the mitotic rate[26]. This reduction of metabolic function affects multiple mechanisms relevant for physiological homeostasis. In this context, it is important to note that postoperative volumetry can be affected by oedema and therefore correlates poorly with postoperative liver dysfunction and functional liver recovery[27].

An increase in portal venous pressure has been postulated as a critical initiator of postoperative liver regeneration[28]. Increased portal inflow, in comparison with liver volume, produces vascular shear stress and increased intrahepatic vascular resistance. This shear stress acts mainly on liver sinusoidal endothelial cells, as it changes levels of sinusoidal perfusion and leads to the release of nitric oxide and other hepatotrophic factors. Nitric oxide primes hepatocytes for proliferation by inhibiting S-adenosyl methionine, which in turn leads to upregulation of cyclins D1 and D2[29,30]. Accumulating evidence suggests that after liver resection, an overwhelming increase in portal pressure results in deleterious effects on liver regeneration[31]. Some authors have even challenged the concept of the 'small-for-size' syndrome and argued that it is rather a 'small-for-flow' process. After transplantation, portal hyperperfusion and sinusoidal congestion are critically involved in hepatic failure[32]. The negative effects of an increase in portal venous pressure are further aggravated by the activation of the hepatic arterial buffer response, with a reduction of hepatic arterial perfusion and concomitant parenchymal ischaemia[33]. In line with this hypothesis, portal venous pressure increase after hepatic resection has recently been documented to correlate with hepatic dysfunction[34]. It is important to note that exploratory evidence has suggested that preoperative portal vein embolization (PVE) might alleviate sudden postresectional increase of portal venous pressure and might have an additional benefit if major resection is planned[34]. Further, changes in hepatic blood flow during liver resection lead to postoperative increased intrahepatic vascular resistance and in turn, to endogenous vasopressor release. An 'acute hepatorenal-like syndrome' because of arterial vasoconstriction can induce acute kidney injury[35]. Around 15 per cent of patients subjected to hepatic resections suffer from acute kidney injury, and this complication is associated with a mortality rate of up to 23 per cent. Through the haemodynamic and haemostatic changes explained above, development of acute kidney injury and hepatorenal syndrome is promoted by PHLF and often ends in multiple organ failure and sepsis.

Initiation of liver regeneration occurs by a combination of several key signalling pathways, including mitogenic growth factors as well as multiple non-mitogenic cytokines. The growth factor receptors of hepatocyte growth factor and epidermal growth factor are key mitogenic receptors for both hepatocytes and progenitor cells[36]. The early phase of liver regeneration is initiated mainly by cytokines. An increase in tumour necrosis factor (TNF)-α activates transcription factors nuclear factor (NF)-κB in Kupffer cells and STAT-3 in hepatocytes[37]. Activated Kupffer cells in turn produce interleukin (IL)-6. IL-6 activates hepatocytes by binding to its receptors initiating proliferation[38]. Downstream activation of IL-6 and TNF-α is also amplified through an increased bacterial translocation into the liver. Bacterial endotoxins and blood-derived enteric microorganisms bind to Toll-like receptors in the liver, which also lead to the expression of these cytokines; however, while endotoxins like lipopolysaccharide induce cytokine expression, increased bacterial load in the liver, mainly because of hepatic inflow occlusion and reduced clearance of toxins, inhibits Kupffer cell function[39,40]. Disturbance of Kupffer cell function can lead to upregulated apoptosis and irreversible necrosis. Overshooting cytokines show a detrimental effect on liver regeneration[41]. An increased inflammatory response can induce systemic inflammatory response syndrome and ultimately end in PHLF and multiorgan failure[42]. An overwhelming immune response may be triggered through excessive bleeding or hepatic in- or outflow exclusion, which can induce hepatic ischaemia–reperfusion injury. Hepatic ischaemia and reperfusion lead to activation of the liver's innate immune system. NF-κB, IL-6, TNF-α, reactive oxygen species, and chemokines are produced by Kupffer and endothelial cells. Although this is intended to facilitate liver regeneration, a disproportionate immune response can aggravate liver injury[43]. An important regulator of surgery-associated inflammatory signals is Kupffer cell plasticity. During the regenerative process, Kupffer cells switch from the pro-inflammatory M1 to the anti-inflammatory, pro-regenerative M2 phenotype. Inhibited phenotype change in Kupffer cells has been shown to negatively impact postoperative liver regeneration and promote occurrence of PHLF[44]. See *Fig. 1* for a schematic presentation of healthy and dysfunctional liver regeneration.

From bench to bedside

Up to now, to study the mechanisms of liver regeneration, animal models have been paramount. The 70 per cent partial hepatectomy model in rodents has given important insights into the physiological processes needed for postresection liver regeneration. A 90 per cent partial hepatectomy seems to approximate the human situation of a severe PHLF and mimics the 'small-for-flow' or 'small-for-size' syndrome[45]. As in humans, extensive resection leads to increased vascular stress and inhibited liver regeneration, due to sinusoidal endothelial cell damage and overshooting inflammation[46]. The use of mouse models has greatly increased the understanding of the role of various genes in human liver regeneration. Through

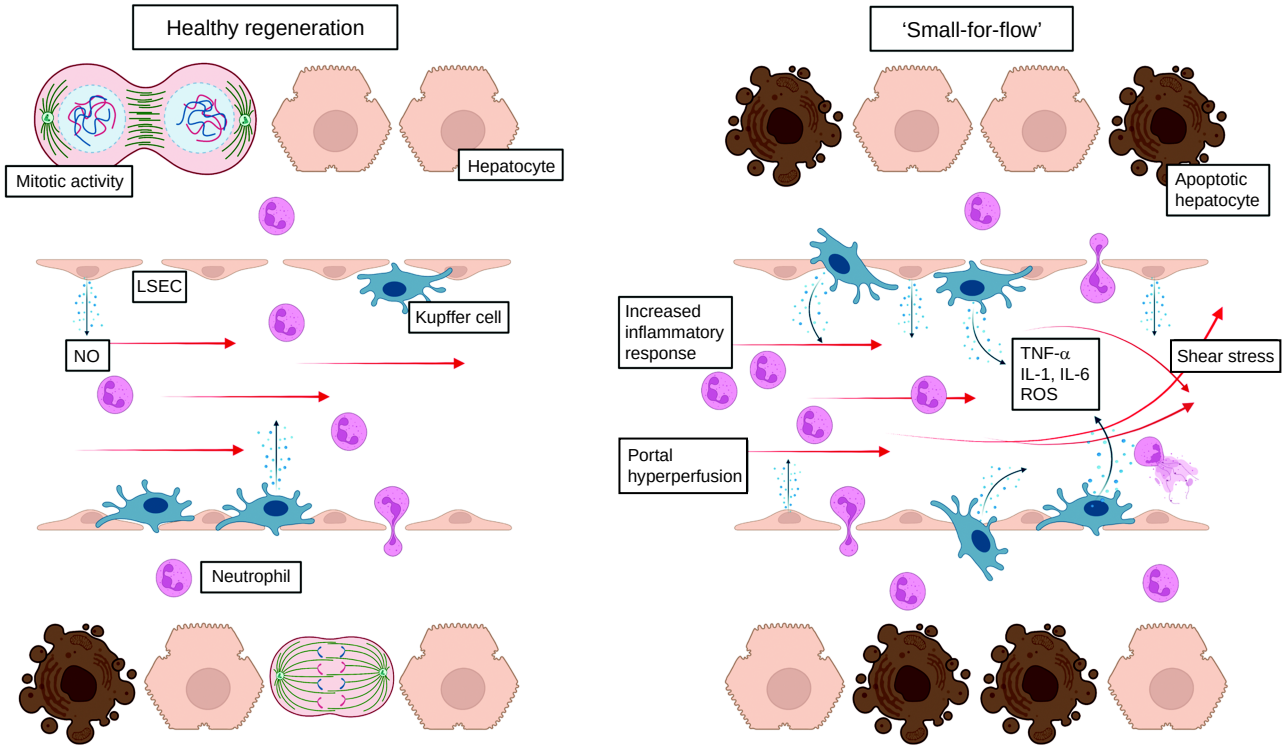

Fig. 1 Schematic overview of normal and dysfunctional liver regeneration

Left side shows functional liver regeneration. Major hepatectomy induces drastic changes in the haemodynamic environment of the liver. An increase in shear stress leads to activation of liver sinusoidal endothelial cells, which in turn release nitric oxide (NO). NO together with cytokines released from Kupffer cells, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 promote liver regeneration. Right side shows dysfunctional liver regeneration. An overwhelming increase in portal pressure can cause 'small-for-flow' syndrome. Excessive shear stress induces an overshooting inflammatory response, followed by neutrophil recruitment into the liver. This causes inhibition of liver regeneration, parenchymal necrosis, and hepatocyte apoptosis. LSEC, liver sinusoidal endothelial cells; ROS, reactive oxygen species.

different transgenic mouse strains, overexpression or depletion of target genes and the associated effect on liver regeneration after partial hepatectomy can be assessed[47]. While animal models have been shown to be very informative, there is still a gap in translation of these data into human relevance.

Clinical risk factors

Parameters associated with PHLF can be categorized into patient-, liver-, or surgery-associated factors. A summary of these factors can be found in *Table 2*.

Patient-associated

- Sex: the likelihood to develop PHLF is almost double in men and the risk of postoperative complications is also generally higher[9]. A possible explanation may be inhibition of immunocompetence through testosterone levels[48]. In a rat model, 17β-oestradiol injection led to accelerated liver regeneration[49]. In a study examining 13,401 patients, the risk for PHLF associated with men was especially pronounced in patients with hepatocellular carcinoma[50]. A possible explanation could be that the incidence of non-alcoholic fatty liver disease in postmenopausal women is higher than in men of the same age. In comparison with other chronic liver diseases such as viral hepatitis or alcoholic steatohepatitis, non-alcoholic fatty liver disease is associated with a lower postoperative risk[50].
- Age: it is still not fully understood how advanced age negatively impacts liver regeneration. With advanced age, bile flow and lower production of acute-phase proteins change and could influence liver regeneration[51]. Another explanation may be that age-related pseudocapillarization in the liver, leading to loss of fenestration in the sinusoidal space, inhibits liver regeneration. In a mouse model, liver regeneration could be rescued by injection of a serotonin receptor agonist, with the hypothesis that serotonin-mediated vascular endothelial growth factor release relaxes the sinusoidal lining[52].
- Sepsis: bacterial endotoxins interact with Kupffer cells and hepatocytes, inhibiting cytokine production needed in the early phase of liver regeneration[53].
- Metabolism: insulin is an important inducer of growth factors such as insulin-like growth factor and hepatocyte growth factor[54]. Animal models have shown that insulin depletion inhibits liver regeneration[55]. BMI and malnutrition also show an association with PHLF[56,57].
- Other: preoperative reduced renal function and cardiopulmonary disease also show a correlation with PHLF[58], presumably as a reflection of the overall physical condition of the patient.

Liver-associated

- Steatosis: hepatic steatosis leads to haemodynamic changes in liver sinusoids leading to an increased risk for ischaemia–reperfusion injury and raises the risk of postoperative complications[59].
- Neoadjuvant chemotherapy: neoadjuvant regimens containing irinotecan or oxaliplatin can cause chemotherapy-associated liver injury and have been shown to have an

Table 2 Risk factors for posthepatectomy liver failure

Patient-associated	
Sex	Risk double in males, especially males with HCC
	Female hormones show proliferative effect in animal models, inhibiting effect of testosterone on immune system
	NAFLD, lower postoperative risk than other chronic liver diseases, higher incidence in postmenopausal women
Age	Still unclear, possible changes in bile flow and acute-phase protein production
	Age-related sinusoidal pseudocapillarization, rescue in animal models through serotonin agonist injection
Sepsis	Bacterial endotoxins decrease cytokine production needed for liver regeneration
	Kupffer cell and hepatocyte function in liver regeneration inhibited
Metabolism	Insulin induces expression of IGF and HGF
	High BMI and malnutrition associated with PHLF
Other	Serum bilirubin, low platelets, insufficient renal function, cardiopulmonary disease, associated with PHLF
Liver-associated	
Steatosis	Leads to changes in the hepatic microenvironment and higher risk for ischaemia–reperfusion injury
Neoadjuvant chemotherapy	Chemotherapy-associated liver injury and steatohepatitis are known complications after neoadjuvant chemotherapy
Fibrosis grade	Functional liver tissue reserve is reduced, patients often present with several comorbidities
Cholestasis	Jaundice increases morbidity after surgery; in animal models, bile duct ligation leads to reduced growth factor expression
Portal hypertension	High preoperative portal pressure in cirrhosis associated with increased risk of PHLF
Surgery-associated	
Future liver remnant	'Small-for-flow' syndrome negatively impacts hepatic haemodynamics
	Increase in portal pressure leads to altered hepatic microcirculation and hepatocyte damage
Blood loss	Leads to intravascular fluid shifts, introduction of bacterial endotoxins into the hepatic microenvironment
	Increased risk of sepsis, coagulopathy and PHLF
Surgical technique	Vascular occlusion can cause ischaemia–reperfusion injury and in increases PHLF risk
	Long Pringle manoeuvre leads to increased oxidative stress and overshooting inflammatory response
	Extensive vascular resection can cause PHLF

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; IGF, insulin-like growth factor; HGF, hepatocyte growth factor; PHLF, posthepatectomy liver failure.

adverse effect on liver physiology and regeneration. Irinotecan has been associated with steatosis as well as steatohepatitis and patients receiving oxaliplatin-containing regimens are more likely to develop sinusoidal obstruction syndrome and biliary complications[60,61].

- Fibrosis grade: the presence of high-grade fibrosis or cirrhosis has a detrimental effect on patient outcome. The risk of fatalities rises with the extent of fibrosis[62]. Patients suffering from high-grade fibrosis or cirrhosis often also present with a plethora of co-morbidities such as portal hypertension, jaundice, or coagulopathy, which all increase PHLF risk[63]. Because of the advanced stage of chronic liver disease, functional liver tissue and liver reserve is reduced[64] resulting in significantly reduced postoperative liver regeneration[65].
- Cholestasis: jaundice can significantly increase the risk of morbidity after surgery[66]. For example, animal models show a decrease in growth factor expression after bile duct ligation, which negatively impacts liver regeneration[67]. In addition, external bile duct drainage might lead to loss of bile salts and influence fibroblast growth factor 19, which could in turn hamper postoperative liver regeneration[68,69].
- Portal hypertension: patients with cirrhosis and portal hypertension have an increased risk of developing PHLF compared with patients with normal portal pressure[70]. Several attempts to predict and prevent PHLF in these patients have been proposed, such as the use of digital twins[71]. More commonly, invasive measurement of the hepatic vein pressure gradient is applied before surgery to predict PHLF[72].

Surgery-associated

- Future liver remnant (FLR): as explained above, 'small-for-flow' syndrome is responsible for drastic haemodynamic changes in the liver. Mainly induced by an intraoperative increase in portal pressure, microcirculation in the liver is altered, and hepatocyte damage occurs[73,74].
- Blood loss: excessive intraoperative blood loss leads to intravascular fluid shifts. This can lead to the introduction of bacteria and bacterial endotoxins to the hepatic microenvironment, increasing the risk of sepsis, coagulopathy, and PHLF. Intraoperative blood loss is directly associated with postoperative morbidity[75].
- Surgical technique: intermittent inflow occlusion or total vascular occlusion are surgical strategies that cause ischaemia–reperfusion injury during hepatic resection, which might increase the risk for PHLF[76]. Mechanistically, during vascular occlusion, Kupffer cells are activated and release pro-inflammatory cytokines such as TNF-α and IL-1 and reactive oxygen species. Lengthy vascular occlusion time leads to increased oxidant stress and immune response after reperfusion. Overshooting inflammatory response and oxidative stress can injure the liver and inhibit liver regeneration. Further, extensive vascular resection and reconstruction of the inferior vena cava has been shown to negatively impact postoperative outcome and cause PHLF. Extensive resection in the portal area and the hepatoduodenal ligament is also associated with PHLF[77]. Frequently used surgical devices in liver resection include the cavitron ultrasonic surgical aspirator and surgical staplers. Studies comparing the two did not show significant differences in postoperative morbidity or blood loss[78]. The stapler technique was, however, shown to be significantly faster than the cavitron ultrasonic surgical aspirator and was associated with lower levels of inflammatory cytokines, possibly due to shorter time under anaesthesia. This study, however, suffered from small a sample size, and a statement about specific mechanisms cannot be made[79]. Furthermore, selecting a

Table 3 Most common methods to assess future liver remnant size

Formula	Method to calculate	Strengths	Limitations
FLR/TLV	(FLR ml/TLV ml)×100	Accurate	Complicated, time-consuming
sFLR	(FLR ml/TELV ml (794–1267×BSA)) ×100	Easy to perform, widely used currently	Potentially inaccurate for large tumours
FLR/BW-ratio	FLR in ml/BW in kg	Easy to perform	Rarely used

FLR; future liver remnant; TLV, total liver volume; sFLR, standardized FLR; TELV, total estimated liver volume; BSA, body surface area; BW, bodyweight.

laparoscopic approach when operating on cirrhotic patients with hepatocellular carcinoma seems to reduce the risk for PHLF compared with open resection[80,81]. In addition, laparoscopic resection of hepatocellular carcinoma in cirrhotic patients with portal hypertension and even Child–Pugh grade B seems feasible[82,83], although high-grade evidence is missing.

Prevention

FLR volume and formulas

The risk of PHLF after liver resection is related to the size of the remnant liver; the smaller the remnant liver, the higher the odds of PHLF[84–86]. Preoperative estimation of liver volume based on three-dimensional reconstructions of contrast-enhanced CT images has been shown to correlate with actual liver weight and is the standard approach to estimate the risk of liver failure after resection[84,87]. FLR volume is usually expressed as the proportion of liver volume that remains after resection relative to the total liver volume excluding tumour volume and is expressed as a percentage as measured on CT images[88]. Alternatively, the measured FLR volume can be related to a calculated total estimated liver volume value using body composition parameters, resulting in a standardized FLR volume. The calculation of total estimated liver volume avoids the segmentation of liver tumours, which can be laborsome[88–90]. Similarly, FLR volume can be related to bodyweight to calculate the remnant liver volume to bodyweight ratio[91]. Despite small differences in predictive values across cohorts, all these calculations aim to guide clinicians towards safe liver resection. *Table 3* describe the most common methods to calculate FLR volume in relation to the total liver volume or other body composition parameters.

Numerous analyses have tried to establish a safe FLR volume cut-off above which PHLF can be avoided. For patients with otherwise healthy liver parenchyma, these cut-offs range from 20 to 30 per cent[92,93]. Most studies report low rates of liver failure (0–6 per cent) when the FLR volume is above the cut-off, and high rates (20–90 per cent) when the FLR volume is smaller[92,94].

For patients with parenchymal liver disease, a similar size liver remnant is compromised in function; and consequently, the risk of PHLF is increased. When liver resection is performed in patients that suffer or have suffered from cholestasis or cirrhosis, the risk of PHLF increases[95,96]. FLR volume is a predictor of PHLF in both cirrhotic and cholestatic patients who undergo liver resection[21,96]. In these patients, a FLR volume of at least 40 per cent is suggested, and some studies recommend even 50 per cent in case of established cirrhosis[21,84,85,95–98]; however, the evidence to substantiate these cut-off levels is limited. The increasing risk of PHLF with a decreasing FLR size is evident. Most studies have tried to establish a cut-off value to select patients for liver resection; yet, the risk of PHLF in a patient with an FLR 1 per cent below any binary cut-off is likely not very different from a patient with a FLR 1 per cent above the same cut-off. Furthermore, the onset of PHLF is multifactorial and many risk factors have been identified, many of which are specific to disease subgroups[99].

FLR volume is perhaps the most important and readily available preoperative parameter to estimate the risk for liver failure, but risk assessment using multiple factors is likely to be essential to truly stratify patients at risk for PHLF.

Methods for preoperative liver function assessment

FLR volume may provide an estimate of the remnant capacity for function and regeneration[100]; however, this only works under the assumption that the total liver function is intact and that its distribution is homogenous. Parenchymal damage and diminished liver function due to chemotherapy or underlying liver disease is not accounted for in normal volumetry and can only be assessed by preoperative liver function tests. In addition, after FLR augmentative procedures such as PVE distribution of function is no longer homogenous and volumetry in these situations is known to both under- and overestimate remnant function[101]. In these circumstances functional tests of the liver have the higher clinical value.

Although the liver is responsible for a wide range of functions, all methods for functional liver assessment focus on one specific part of liver function as a predictor of actual global liver function and of regenerative potential. For practical use, a test should be able to estimate the risk of PHLF, assess the need for FLR augmentative procedures, and be used to estimate the effect after such procedures. Based on the aforementioned practical issues with volumetry, two parts of functional tests are essential: estimation of total liver function and its distribution in the FLR. When both are combined, this leads to an estimate of the actual remnant function as a potential predictor for PHLF.

Laboratory tests and models such as ALBI and Model for End-stage Liver Disease provide screening tools for poor liver function but are only useful in the low range of total function[102]. The same can be said about the use of biopsies and elastography[103]. This makes these tests of limited value for providing information on the FLR function. Nevertheless, because of low costs and high availability, simple laboratory tests can be used as a screening tool for poor general liver function or limited regenerative potential due to an underlying liver condition.

A wide range of tests and imaging methods is available to measure liver function before surgery (*Table 4*). There are no randomized trials or high-level evidence to support the use of any of these tests to predict PHLF better than volumetry; however, based on retrospective series and use in daily practice, there is consensus among experts that functional assessment of the remnant liver is essential for predicting PHLF in compromised and FLR-augmented livers (with European consensus guidelines in preparation). To understand the value

Table 4 Overview preoperative tests to estimate adequate remnant liver function

Test	Agent used	FLR volume	TL function	FLR function	Distribution	FLR function after	Complexity	Validated for PHLF
Volumetry		Yes	No	No	No	–	–	++
Laboratory scores		No	No*	No	No	–	–	+
ICG test	Indocyanine green	No	Yes	No	No	–	+	++
LIMAX	^{13}C-methacetin	No	Yes	No	No	–	+	+
LIMAX+volumetry	^{13}C-methacetin	Yes	Yes	Yes	No	+	++	+
ICG+volumetry	Indocyanine green	Yes	Yes	Yes	No	+	++	++
HBS	^{99m}Tc-Mebrofenin	Yes	Yes	Yes	Yes	++	++	++
RLE-MRI	Gadoxetic Acid	Yes	Limited†	Limited†	Yes	+†	+	+
DCE-MRI	Gadoxetic Acid	Yes	Yes	Yes	Yes	++	+++	–

ICG, Indocyanine green; HBS, hepatobiliary scintigraphy; RLE, relative liver enhancement; MRI, magnetic resonance imaging; DCE, dynamic contrast-enhanced; FLR, future liver remnant; TL, total liver; PHLF, posthepatectomy liver failure; +, low; ++, medium; +++, high. *Only sensitive in low liver function/cirrhosis. †Not absolute.

of functional tests, it is important to explain the mechanisms behind commonly used methods, their respective advantages, and their drawbacks. First, there are tests that measure clearance or metabolism of a certain substance. The outcome is calculated in a multi-compartment model, and the outcome gives a measure of total function[104,105]. Examples are the indocyanine green (ICG) clearance and LIMAX (^{13}C-methacetin breath) metabolic tests[106,107]. As the goal is to estimate FLR function, total liver function tests should always be accompanied by volumetric correlation, dividing the total function by the remnant volume share under the assumption of homogeneity of distribution within the liver. After FLR augmentative procedures, this method cannot measure the effect of the intervention on FLR function as it only gives information on total function and not regional functional distribution. A second group of tests combines clearance of an imageable agent, for instance ^{99m}Tc-Mebrofenin or ^{99m}Tc-GSA (DTPA-galactosyl serum albumin) and gadoxetic acid, with a three-dimensional structural scan (for hepatobiliary scintigraphy (HBS) and MRI)[108–111]. These methods provide accurate information about distribution of function, which is a clear advantage over total liver function tests; however, routine use is not widely adopted due to the complexity of acquisition, processing, and interpretation. The advantage of the MRI technique is that it could potentially serve as a one-stop-shop solution, providing structural diagnostic scans and functional information in one examination. A potential, but unusual, limitation is that some patients do not tolerate MRI scanning due to severe anxiety[112]. Basically, there are two ways that MRI can be used for clearance-based assessment. The most straightforward method is to measure relative enhancement of the liver compared with another organ, such as the spleen or muscle. In daily practice, this method seems to be able to predict PHLF quite well[110]; however besides the influence of flow and cardiac output, the technical nature of MRI scanning implies that measured values are, by definition, estimated and not absolute. The patient as well as the multitude of different types of MRI scanners and vendors combined with local conditions further complicate inter-patient and inter-centre comparability. The result is an uncalibrated value of enhancement, and thus a function measurement that cannot be compared between patients and no clear cut-offs for safe resections can be given. An alternative to relative methods is to measure the clearance over time using a dynamic scanning protocol. This provides a slope 'K-value', and therefore, an actual estimate of the speed of clearance and more closely resembles other clearance measurements (such as the ICG test or HBS); however, these protocols require longer acquisition times, are highly complex and difficult to implement[110]. Hepatobiliary scintigraphy is based on clearance of an isotope-labelled, liver-specific agent such as ^{99m}Tc-Mebrofenin[113]. Processing is similar to a dynamic MRI, however, acquisition is much less complex[108]. Interpretation is straightforward, and due to good comparability between centres, it has been validated more systematically, which has led to a practical clinical cut-off value[114]. When combined with single-photon emission CT, some anatomical mapping and FLR calculation can also be acquired[115], although with clearly inferior quality compared with MRI. All described clearance methods may suffer from accumulation of the cleared agent in the bile ducts, and masking of this signal is sometimes needed to compensate for interference. This significantly adds to the complexity of the processing and interpretation[108]. Another drawback is that the clearance may be hampered in patients with cholestasis[116]. The transporter proteins are dysregulated, and the agent must compete with bilirubin for transport in and out from the hepatocyte resulting in a low measure of function. This does not mean that the measurement is impossible to use in jaundiced patients, it just clearly shows that these patients suffer from hepatic dysfunction. After biliary drainage and restoration to normal levels of bilirubin, the test can be repeated and should show a normalized function, more accurately resembling the actual postoperative remnant function. An alternative for ^{99m}Tc-mebrofenin is ^{99m}Tc-GSA. ^{99m}Tc-GSA is albumin-bound and liver specific and not dependent of bilirubin levels, making its application less complicated in jaundiced patients; however, GSA is not registered in most western countries, limiting its use. The information on regional distribution of function supplied by HBS and MRI can be very useful in jaundiced or insufficiently drained patients, showing dysfunctional or poorly drained segments that may require further interventions to improve remnant function. *Fig. 2* shows a ^{99m}Tc-Mebrofenin scan with poor biliary drainage of the right posterior sector, remnant function was below the safe threshold for resection and improved sufficiently after additional biliary drainage.

For practical use, volumetry combined with a general functional test as screening tool for a compromised liver might work well in daily practice; however, when augmentative procedures are used, the advantage of imaging of distribution of function is evident and more complex methods are required. Choice of functional modality depend largely on local availability and expertise.

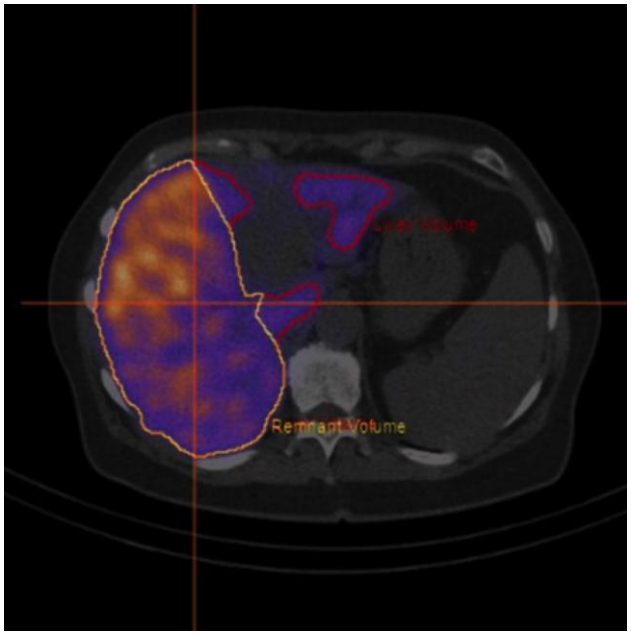

Fig. 2 Regional distribution of liver function assessed with hepatobiliary scintigraphy

^{99m}Tc-mebrofinin scan showing poor drainage of the right posterior sector, as can be seen by the higher (yellow signal) compared with low (blue).

Modulation of the FLR

When the remnant liver is deemed insufficient for safe liver resection, a preoperative procedure to increase the liver remnant volume, and hopefully the corresponding function, can be performed. Preoperative PVE is the most accepted approach. The embolization of the portal branches to the segments intended for resection results in a compensatory growth of the FLR. While there are many studies on PVE that focus on the hypertrophic response and outcome after surgery following PVE, true comparative analysis on the impact of PVE on liver failure are sparse[117–119]. In the only prospective trial to date, PVE was associated with fewer complications in patients with chronic liver disease, but not in those with normal liver parenchyma; however, the trial did not include an FLR cut-off for inclusion, and the mean FLR volume was 30 per cent before PVE which might indicate that study population was not at a high risk of liver failure. Indeed, there was no liver failure in patients with normal liver parenchyma, and only two patients with liver failure in the chronic liver disease group, one with and one without PVE[120]. In patients with biliary tumours who have a high risk of liver failure, a matched study showed that PVE was associated with substantial reductions in PHLF rates[121]. Indeed, a more liberal approach towards PVE in these patients probably results in better outcomes[122,123]. Most other studies are non-comparative studies that show that liver resection can be performed with acceptable outcomes in patients in whom resection was not feasible without PVE[124–128]. The ability of the FLR to grow after PVE has been identified as an important predictor of a good outcome after resection[129]. When limited FLR growth is observed after PVE, subsequent resection has been shown to be associated with poor outcomes and can be a reason not to proceed to surgery. While tumour progression is the main reason for patients not to proceed to surgery after PVE, the absence of hypertrophy in some patients has fuelled the search for more effective liver regenerative strategies.

Before the introduction of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), two-stage hepatectomies had been used for more than a decade[130,131]. ALPPS is an accelerated two-stage procedure, combining portal vein occlusion with (partial) parenchymal transection to induce a rapid growth of the FLR[132]. The rapid hypertrophy allows for an earlier final resection, thereby increasing the resection rate compared with that of PVE[133,134]. Yet, liver failure and mortality rates remain higher with ALPPS despite the rapid liver growth[133,135]. Interestingly, none of the parameters on liver growth are related to postoperative outcomes. Only baseline FLR size is correlated to the overall outcomes[136]. Therefore, it can be argued that to make ALPPS safer, PVE should be attempted first to minimize the risk of PHLF[137,138]; however, such an approach would probably result in a lower resection rate, but it can be questioned whether the resection rate is worth the high 90-day fatalities[134,139], even if recent publications on the use of ALPPS in patients with colorectal liver metastases show improved safety compared with initial series[140].

In the search for more and faster hypertrophy without the increased risk of liver failure and fatalities seen in ALPPS, a simultaneous PVE and hepatic vein embolization (HVE) has emerged as promising alternative[141]. This combination (PVE/HVE) means that PVE (generally right-sided) is combined with occlusion of the hepatic vein that drains the deportalized side of the liver. Although it is thought that PVE/HVE results in greater hypertrophy compared with PVE alone, comparative studies have still not shown a difference[42–146]. Resection rates and outcomes after resection following PVE/HVE were also similar to PVE alone[147]. PVE/HVE seems a safe alternative, and future studies should show whether this new technique provides a benefit over PVE alone. Radiological examples of PVE, ALPPS, and PVE/HVE are depicted in *Fig. 3*.

Intraoperative and postoperative techniques for prevention of PHLF

Pringle manoeuvre

The Pringle manoeuvre was initially described to temporarily occlude the inflow to the liver with a soft clamp to control bleeding from the liver injury in the setting of liver trauma[148]. Over the years, liver surgeons widely adopted the Pringle manoeuvre in liver resection surgery and demonstrated reduced intraoperative bleeding and operative time[149,150]; however, ischaemia followed by reperfusion of the liver has been argued to cause injury to the hepatocyte metabolism[151], resulting in cytolysis. The ischaemia–reperfusion injury results in insufficient hepatic synthesis of acute-phase proteins and coagulation factors. The resulting changes in the inflammatory cascade increase the rates of posthepatectomy liver dysfunction and an impaired immune defence against bacterial infections[152–154]. Splanchnic vascular stasis due to the Pringle manoeuvre also damages enterocytes, loss of gut barrier, and contributes to endotoxaemia[155]. The increased bacterial translocation and endotoxins to the liver from portal circulation directly affect liver regeneration by impairing the initiator cytokines and causing direct damage to hepatocytes, resulting in cellular death. Ischaemic preconditioning has been proposed to be beneficial in animal models[156], but its potential benefit remains to be demonstrated more clearly in humans[57]. Several randomized clinical trials investigated whether an intermittent Pringle manoeuvre would reduce some of the detrimental effects of a continuous Pringle manoeuvre; however, most of the

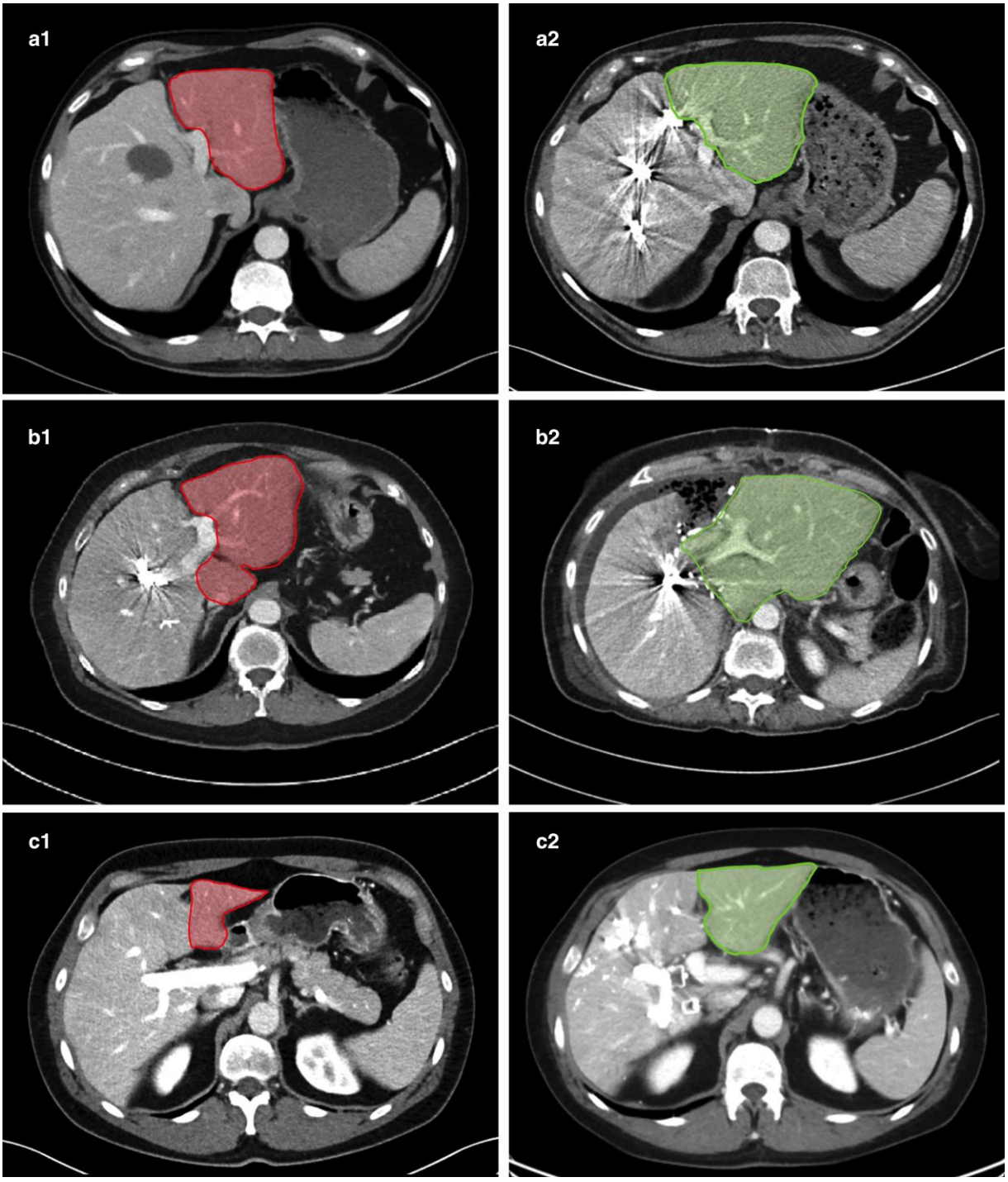

Fig. 3 Methods to increase future liver remnant size

Contrast-enhanced CT of patients subject to different treatments. **a** PVE. **b** Rescue ALPPS after insufficient effect of PVE. **c** PVE/HVE. Before (1) and after (2) images are shown in each case. All patients with left lateral segment (plus/minus segment 1) as FLR marked with red before intervention and green at evaluating radiology. PVE, portal vein embolization; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; HVE, hepatic vein embolization; FLR, future liver remnant.

studies failed to demonstrate clinically significant benefits of an intermittent over continuous Pringle manoeuvre[158], while some studies continue to caution against the Pringle manoeuvre[159,160]. Fagenson *et al.*[159], in a propensity-matched study, reported increased rates of PHLF and septic shock with the use of the Pringle manoeuvre for partial hepatectomies. Hemihepatic vascular inflow occlusion on the ipsilateral side of resection after isolating the vessels is reported to be better tolerated[161]. Ishizuka *et al.* reported shorter postoperative survival with longer Pringle manoeuvre time in patients undergoing resection for hepatocellular cancer[162]. Huang *et al.*[163] compared a 25-min intermittent Pringle manoeuvre with a 15-min occlusion for resection of hepatocellular carcinoma. They reported a higher speed of liver transection (1.38 *versus* 1.23 cm^2/min, $P = 0.002$) and lower blood loss during transection (109 *versus* 166 ml, $P < 0.001$) than the 15-min intermittent Pringle manoeuvre group. The authors of the present review do not believe that using the Pringle manoeuvre is mandatory for achieving good outcomes in

liver resection, nor that it negatively influences outcomes when applied shortly. When the Pringle manoeuvre is used, the preference should be for judicious use of intermittent Pringle, preferably selective to the side of resection and for the shortest duration of parenchymal transection.

Intraoperative blood loss

Blood loss during liver surgery is determined by the complexity of liver resection, background liver parenchymal characteristics such as the presence of steatohepatitis or chemotherapy-induced liver injury, and the individual surgeon's experience. Intraoperative blood loss of more than 1200 ml and the need for perioperative blood transfusion are considered risk factors for PHLF[164]. The haemodynamic instability due to blood loss results in ischaemia–reperfusion injury. The need for blood transfusions results in potential immunosuppressive effects. With appropriate measures of low central venous pressure, judicious use of energy devices, and cavitron ultrasonic surgical aspirator, blood loss can be kept to a minimum.

Haemostasis and bile leaks to prevent postoperative sepsis

Sepsis is one of the common causes of death in patients with established PHLF. In addition, patients with liver failure are prone to develop sepsis, and sepsis due to any cause can also exacerbate PHLF[12]. The hypodynamic circulation and multiple organ failure associated with sepsis can result in hypoperfusion of the remnant liver, and it can further reduce the functional mass of Kupffer cells that play a pivotal role in the cytokine and IL regulation required for liver regeneration. Postoperative sepsis could be due to multi-site and multifactorial issues, of which intra-abdominal collections due to infected hematomas and biliary collections are some of the common causes. Meticulous haemostasis and attention to biliary stasis are essential in preventing postoperative collections following major liver resections. Several intraoperative measures such as transcystic air leak test[165], portal re-occlusion[166], and white test with lipid solution[167] were described for localizing leaking biliary radicles on the transection surface. These tests can be used to identify and control the bile leak so the risk of postoperative biloma is reduced. As bile salt depletion could also affect liver regeneration negatively, large amount of externally drained bile (found and drained after surgery) should probably be returned to the patients enteric circulation[68].

Flow modulation

It is increasingly realized that PHLF is not only a small remnant volume issue. The function of the FLR and the portal flow are also realized to be part of the pathophysiological process. The mechanics of hepatic inflow form the basis for applying modulatory flow principles and are implied in liver resections to reduce the risk of liver dysfunction. Portal flow modulation techniques, including portal flow diversion, splenic artery ligation, and splenectomy have long been applied in living-donor liver transplantation. Increased flow and pressure in the portal vein result in shear stress on sinusoidal endothelial cells that release nitric oxide, promoting liver regeneration. Ironically, excessive portal venous flow for the volume of the liver parenchyma leads to increased sinusoidal pressure, endothelial damage, and sinusoidal haemorrhage. High portal vein pressures also result in hepatic artery buffer response by reducing hepatic artery pressures leading to ischaemic biliary injury[168]. Regenerative response of the liver requires a balanced increase in the portal venous flow leading to regenerative stimulation but not up to the onset of hepatocytes injury. In addition, a reduced portal venous flow stimulates the hepatic arterial buffer response resulting in an increased hepatic tissue pO_2 due to raised arterial flow and improved liver regeneration in animal studies[169]. Troisi *et al.*[170] reported, and it is widely adopted, that a portal venous flow rate of more than 250 ml/min/100 g or a portal venous pressure of more than 20 mmHg is associated with poor outcomes. These detrimental effects get augmented when the liver volumes are less than optimal.

Splenectomy and splenic artery ligation

Splenic blood flow contributes to 25–30 per cent of the total portal flow. The percentage contribution of splenic flow to the remnant liver is much higher following major hepatectomy resulting in increased portal pressures. The role of splenectomy in flow modulation and preventing liver dysfunction is well described in living-donor liver transplantation; however, its role in extended hepatectomies is only described in animal studies. Splenectomy increases vascular compliance and hepatic serotonin levels, which improve hepatic perfusion through its vasodilatory effect. Serotonin exerts a protective effect by increasing microcirculation and accelerating liver regeneration by stimulating endothelial cells to release vascular endothelial growth factors[171,172]. Splenectomy enhances DNA synthesis and proliferation of cell nuclear antigens to facilitate liver regeneration in rats undergoing major hepatectomies. Risks of splenectomy include intraoperative bleeding, opportunistic postsplenectomy infection, and the need for long-term antibiotics. Splenic artery ligation is also an effective way to reduce the portal venous pressure and increase hepatic artery flow[173]. The arterial inflow from short gastric arteries will help preserve splenic parenchyma, although splenic infarction, splenic abscess, and pancreatitis have been described.

Pharmacological intervention of portal venous flow

Pharmacological modulation of portal venous flow using somatostatin analogues such as octreotide were explored as an alternative to splenectomy and splenic artery ligation. Somatostatin blocks the SSTR2 receptors on the endothelial cells of splanchnic vasculature resulting in vasoconstriction, reduced splanchnic flow, and decreased portal venous pressure. In addition, it suppresses hepatocellular proliferation but encourages a more regular and orderly regeneration. An intraoperative bolus dose of somatostatin bolus (250 μg) followed by a continuous 250 μg/h infusion for 5 days was used[174]. Animal studies have shown a marked reduction in portal venous flow and pressure and attenuation of liver injury after 80 per cent and 90 per cent hepatectomies with rapid and effective flow modulation[175–177]. In smaller clinical studies, when portal venous pressure is greater than 20 mmHg, somatostatin has immediately reduced the pressures by 2.5 mmHg[174]. Whether this translates to significant clinical benefit needs to be assessed in the larger ongoing clinical trials (such as SOMAPROTECT01; registration number: NCT02799212, http://www.clinicaltrials.gov). Another randomized clinical trial evaluated whether terlipressin could influence postoperative outcome after liver resection, without demonstrating a positive effect in the intervention arm[178].

Intraoperative N-acetylcysteine administration

To limit oxidative cellular injury, *N*-acetylcysteine infusion has been used to clear (scavenging) the excess oxygen free radicles produced due to ischaemia–reperfusion injury[179]; however,

clinical studies failed to demonstrate a clinical benefit of its use[180,181]. Timing of the administered treatment and limited sample size in these trials might have influenced the results negatively.

Intraoperative steroids

Glucocorticoids are potent anti-inflammatory drugs that modulate inflammatory and anti-inflammatory pathways. The role of steroids in altering the inflammatory pathways that can lead to systemic inflammatory response syndrome was evaluated in several randomized clinical trials[182–185]. Methylprednisolone 500 mg before induction or up to 90 min before surgery was used. These studies have demonstrated favourable postoperative changes in laboratory markers of systemic inflammation, including IL-6, IL-10, TNF-α, C reactive protein, liver function tests, and prothrombin time. In a meta-analysis by Richardson *et al.*[186], preoperative steroids were associated with statistically significant reductions in serum bilirubin and IL-6 in the early postoperative interval. There was a trend towards a lower incidence of postoperative complications and prothrombin time, but it did not reach statistical significance.

Treatment

In general, current treatment recommendations for severe PHLF are based on treatment algorithms developed to support patients with acute liver failure due to other reasons than PHLF[187]. The most important goal is to support organ function, and thus, provide a chance for the failing liver the recover spontaneously. Symptomatic treatment for PHLF include all aspects of modern organ and patient support available at specialized intensive care units. This has been described extensively before and will not be repeated in this review[31,188,189]. In the following section specific aspects of PHLF treatment regarding medical treatment, extracorporeal liver support systems, and liver transplantation (LTx) will be discussed.

Medical/cell-derived treatment

Presently, there is not a single drug, nor a combination of different agents available to cure patients with PHLF; however over the past years, several treatment strategies have been evaluated. Some of them, such as aggressive treatment of infectious complications are established and uncontroversial, whereas others might be considered experimental.

Antibiotics

Appropriate steps must be taken to prevent postoperative sources of infection. Early mobilization, fast return to oral intake, and early removal of drains as part of an enhanced recovery programme showed a reduction in the risk of infectious complications[190]. Early recognition of sources of sepsis with appropriate radiological imaging, drainage of infected collections, and appropriate antibiotics are all important in controlling the infection that could induce or aggravate PHLF[191]. A recent meta-analysis found no benefit in postoperative prophylactic administration of antibiotics in patients following hepatectomy in terms of rate and fatalities[192]; however when PHLF is diagnosed, aggressive antimicrobial treatment is advised as infectious complications and sepsis are both common in PHLF, increasing the risk for adverse patient outcomes[193].

Lactulose

Hepatic encephalopathy is a severe complication in patients with PHLF, mainly triggered by increased ammonia due to insufficient metabolism in the liver[194]. Treatment for patients with PHLF follows the same recommendations for treatment as patients with acute liver failure, and high-dose lactulose is recommended routinely[94].

Stem cells

Even though stem cell therapy might not be considered a classical medical treatment, it probably represents one of the most promising treatment alternatives for patients with PHLF in the future. Over the past years numerous publications have been addressing different treatment aspects, mainly in liver diseases such as fibrosis[195] and end-stage liver disease[196]. Results following mesenchymal stem cell transplantation in a porcine hepatectomy model have shown promising results[197,198]; however, this treatment presently has not reached clinical practice, and several limitations remain critical, such as target-organ infiltration and the number of administered cells[199].

Extracorporeal liver support

Theoretically, extracorporeal liver support systems represent an appealing approach to bridge an impaired liver function in the immediate postoperative phase; however, these devices are mainly developed to support failing liver function in patients with acute or acute-on-chronic liver failure[200]. For these patients, it was hypothesized that the removal of not only water-soluble but also albumin-bound toxins would assist in detoxification and support global liver function until recovery. The first available device was the molecular adsorbent circulating system (MARS)[201,202]. MARS treatment has demonstrated improved liver detoxification and haemodynamics in patients with both acute and acute-on-chronic liver failure[203,204]; however, MARS treatment did not result in improved survival in two large randomized clinical trials, neither in acute-on-chronic[205] nor in acute liver failure[206]. Other techniques, such as the single-pass albumin dialysis and plasma separation and filtration, have been developed[207] and demonstrated comparable results to MARS in terms of their detoxification capacity[200,208,209]. In contrast, high-volume plasma exchange achieved improved transplant-free survival in patients with acute liver failure in a randomized clinical trial[210]. In the PHLF setting, however, only the MARS system has been systematically evaluated. In a prospective study, MARS was found to be safe and feasible to use in patients with PHLF early after hepatectomy[211]; however in a systematic review, it was not possible to provide evidence to support a routine use of MARS in patients with PHLF[212]. Other devices, such as bioartificial liver support systems, could potentially increase the benefit of extracorporeal liver support systems, adding additional hepatic functions like synthesis of proteins and coagulation factors on top of the detoxification. In 2004, a randomized clinical trial evaluating a porcine hepatocyte-based bioartificial liver support system in patients with acute liver failure could not demonstrate a significant survival benefit for the patients in the intervention arm[213]. Since then, different systems have been developed, mainly based on porcine derived hepatocytes[214]. Due to legal reasons in many countries, there is a need to use human-derived hepatocytes in bioartificial liver support systems because xenotransplantation is widely prohibited. Such systems are currently under evaluation in both animal and human studies but are not yet available for routine clinical use[215].

Liver transplantation and PHLF

Liver transplantation is frequently stated to be the only definite treatment in patients with PHLF; however, the scientific evidence is low, and there are many obvious limitations. So far, three articles have described the experience with LTx in PHLF, two single-centre series[216,217] and a recent multicentre experience[218]. All concluded that it is safe and feasible to offer LTx to patients with PHLF with good long-term outcomes comparable to LTx for established indications; however, there are many unanswered questions such as the optimal time point for LTx and how to justify this indication in light of donor organ shortages. Thus, LTx will probably remain a rescue treatment in expert centres for patients with benign histopathology or a diagnosis already accepted for LTx even without PHLF (for example hepatocellular cancer according to national guidelines). To provide access to LTx for patients with PHLF, it is necessary to have national strategies as well as established cooperation between liver transplantation units and hospitals performing hepatectomies.

Discussion and future perspectives

In this review, the evidence for the most important aspects on PHLF has been summarized. Evident to the reader is the absence of high-grade evidence for most aspects of PHLF research. Furthermore, the lack of accurate tools to predict PHLF and effective treatment adds to the clinical challenge of PHLF for hepatobiliary surgeons worldwide.

As seen in this review there are countless attempts to define PHLF. In the paper where the ISGLS PHLF criteria were presented for the first time, Rahbari *et al.* listed almost 50 different publications with its own corresponding definition of PHLF between 2003 and 2009[3]. Since then, numerous additional articles presenting new definitions of PHLF have been published, many of them originating from single centres without validation. Whether this is a result of a disagreement with the ISGLS criteria or a real effort to improve the definition of PHLF is presently unclear. In 2017, Skrzypczyk *et al.* published an article comparing the ISGLS, Balzan 50:50 and peak bilirubin criteria with regard to their value in predicting severe outcomes related to PHLF[219]. This article was commented on by Harrison *et al.*[220], discussing potential flaws of studies comparing binary predictive scoring systems, both from a statistical and clinical point of view. The following reply by Skrzypczyk *et al.*[221], however, vividly demonstrate the lack of agreement on PHLF-related questions in the hepatobiliary surgical community. From a clinical point of view, it would be desirable to have a definition for every patient undergoing hepatectomy, with high accuracy and applicable as early as possible after surgery, to guide the surgeon in selecting early postoperative treatment strategies (that are currently lacking); however, the implementation of a new definition should be counselled by an organization such as ISGLS or International Hepato-Pancreato-Biliary Association and not by several individual single centres. So, the recommendation until then is to urge the hepatobiliary community to use the ISGLS criteria in publications on PHLF to allow comparison between studies.

Liver volume measurements are the cornerstone to estimate the risk before surgery of PHLF after liver resection. Despite the great number of studies, most studies focus on a binary volume cut-off, whereas the risk of PHLF gradually increases with a decreasing FLR size. Furthermore, data on very large cohorts remain limited, and future international collaborative prospective trials might be the way forward. Most research on liver regenerative procedures focusses on the extent and speed of liver growth and the resection rate. Yet, it remains to be established whether an increased resection rate also provides an oncological benefit or whether the test of time that prevents surgery in patients with unfavourable tumour biology is more important.

The development of an accurate and easily available liver function test with capacity to measure regional function would probably be the most important tool to prevent PHLF. This could assist the hepatobiliary surgeon not only in avoiding resection in patients with limited FLR function (or submit them for FLR-augmenting procedures) but also potentially reveal sufficient FLR function in patients that today are deemed unresectable with current methods.

Given the relevant differences between mice and men, identification and characterization of pathophysiological processes dysregulated in patients developing PHLF is key to identify potential new treatment targets. Clinically applicable, integrative models, including preoperative modifiable and non-modifiable risk factors, might improve preoperative risk assessment in patients undergoing hepatic resection.

Funding

The authors have no funding to declare.

Disclosure

The authors declare no conflict of interest.

Data availability

This is narrative review and no data have been generated by the authors.

References

1. Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Stromberg C. Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden-a population-based study. *Langenbecks Arch Surg* 2017;**402**:105–113
2. Gilg S, Sandstrom P, Rizell M, Lindell G, Ardnor B, Stromberg C *et al.* The impact of post-hepatectomy liver failure on mortality: a population-based study. *Scand J Gastroenterol* 2018;**53**:1335–1339
3. 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
4. Michalopoulos GK. Liver regeneration. *J Cell Physiol* 2007;**213**: 286–300
5. Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. *Nat Rev Gastroenterol Hepatol* 2021;**18**:40–55
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; **10**:89.

7. Stone HH, Long WD, Smith RB, 3rd Haynes CD. Physiologic considerations in major hepatic resections. *Am J Surg*. 1969; **117**:78–84
8. 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 8–9
9. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S *et al.* Hepatic insufficiency and mortality in 1059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007; **204**:854–862; discussion 62–4
10. Calthorpe L, Rashidian N, Benedetti Cacciaguerra A, Conroy PC, Hibi T, Hilal MA *et al.* Using the comprehensive complication index to rethink the ISGLS criteria for post-hepatectomy liver failure in an international cohort of major hepatectomies. *Ann Surg* 2021
11. Baumgartner R, Gilg S, Bjornsson B, Hasselgren K, Ghorbani P, Sauter C *et al.* Impact of post-hepatectomy liver failure on morbidity and short- and long-term survival after major hepatectomy. *BJS Open* 2022;**6**:zrac097
12. van Keulen AM, Buettner S, Besselink MG, Busch OR, van Gulik TM JNMIJ *et al.* Primary and secondary liver failure after major liver resection for perihilar cholangiocarcinoma. *Surgery* 2021; **170**:1024–1030
13. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am J Pathol* 2010;**176**:2–13
14. Niederwieser T, Braunwarth E, Dasari BVM, Pufal K, Szatmary P, Hackl H *et al.* Early postoperative arterial lactate concentrations to stratify risk of post-hepatectomy liver failure. *Br J Surg* 2021;**108**:1360–1370
15. Rahbari NN, Reissfelder C, Koch M, Elbers H, Striebel F, Buchler MW *et al.* The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. *Ann Surg Oncol* 2011;**18**:3640–3649
16. Sultana A, Brooke-Smith M, Ullah S, Figueras J, Rees M, Vauthey JN *et al.* Prospective evaluation of the International Study Group for Liver Surgery definition of post hepatectomy liver failure after liver resection: an international multicentre study. *HPB (Oxford)* 2018;**20**:462–469.
17. Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H *et al.* Mortality after liver surgery in Germany. *Br J Surg* 2019;**106**: 1523–1529
18. Starlinger P, Ubl DS, Hackl H, Starlinger J, Nagorney DM, Smoot RL *et al.* Combined APRI/ALBI score to predict mortality after hepatic resection. *BJS Open* 2021;**5**:zraa043
19. Dasari BVM, Hodson J, Roberts KJ, Sutcliffe RP, Marudanayagam R, Mirza DF *et al.* Developing and validating a pre-operative risk score to predict post-hepatectomy liver failure. *HPB (Oxford)* 2019;**21**:539–546
20. Shi JY, Sun LY, Quan B, Xing H, Li C, Liang L *et al.* A novel online calculator based on noninvasive markers (ALBI and APRI) for predicting post-hepatectomy liver failure in patients with hepatocellular carcinoma. *Clin Res Hepatol Gastroenterol* 2021; **45**:101534
21. Prodeau M, Drumez E, Duhamel A, Vibert E, Farges O, Lassailly G *et al.* An ordinal model to predict the risk of symptomatic liver failure in patients with cirrhosis undergoing hepatectomy. *J Hepatol* 2019;**71**:920–929
22. Starlinger P, Hackl H, Pereyra D, Skalicky S, Geiger E, Finsterbusch M *et al.* Predicting postoperative liver dysfunction based on blood-derived MicroRNA signatures. *Hepatology* 2019;**69**:2636–2651
23. Starlinger P, Pereyra D, Haegele S, Braeuer P, Oehlberger L, Primavesi F *et al.* Perioperative von Willebrand factor dynamics are associated with liver regeneration and predict outcome after liver resection. *Hepatology* 2018;**67**: 1516–1530
24. Truant S, El Amrani M, Skrzypczyk C, Boleslawski E, Sergent G, Hebbar M *et al.* Factors associated with fatal liver failure after extended hepatectomy. *HPB (Oxford)* 2017;**19**:682–687
25. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 2010;**97**:1260–1268
26. Kobayashi T, Imamura H, Aoki T, Sugawara Y, Kokudo N, Makuuchi M. Morphological regeneration and hepatic functional mass after right hemihepatectomy. *Dig Surg* 2006; **23**:44–50
27. Kwong AJ, Goel A, Mannalithara A, Kim WR. Improved posttransplant mortality after share 35 for liver transplantation. *Hepatology* 2018;**67**:273–281
28. Yokoyama Y, Nagino M, Nimura Y. Mechanisms of hepatic regeneration following portal vein embolization and partial hepatectomy: a review. *World J Surg* 2007;**31**:367–374
29. Matsumoto K, Yoshitomi H, Rossant J, Zaret KS. Liver organogenesis promoted by endothelial cells prior to vascular function. *Science* 2001;**294**:559–563
30. Kin Y, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M *et al.* Doppler analysis of hepatic blood flow predicts liver dysfunction after major hepatectomy. *World J Surg* 1994;**18**: 143–149
31. van Mierlo KM, Schaap FG, Dejong CH, Olde Damink SW. Liver resection for cancer: new developments in prediction, prevention and management of postresectional liver failure. *J Hepatol* 2016;**65**:1217–1231
32. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant* 2005;**5**: 2605–2610
33. Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K *et al.* Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. *Am J Surg Pathol* 2006;**30**:986–993
34. Bogner A, Reissfelder C, Striebel F, Mehrabi A, Ghamarnejad O, Rahbari M *et al.* Intraoperative increase of portal venous pressure is an immediate predictor of posthepatectomy liver failure after major hepatectomy: a prospective study. *Ann Surg* 2021;**274**:e10–e17
35. Reiterer C, Taschner A, Luf F, Hecking M, Tamandl D, Zotti O *et al.* Effect of liver resection-induced increases in hepatic venous pressure gradient on development of postoperative acute kidney injury. *BMC Nephrol* 2022;**23**:21
36. Michalopoulos GK. Hepatostat: liver regeneration and normal liver tissue maintenance. *Hepatology* 2017;**65**:1384–1392
37. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. *Hepatology* 2006;**43**:S45–S53
38. Garcea G, Maddern GJ. Liver failure after major hepatic resection. *J Hepatobiliary Pancreat Surg* 2009;**16**:145–155
39. Sakamoto T, Liu Z, Murase N, Ezure T, Yokomuro S, Poli V *et al.* Mitosis and apoptosis in the liver of interleukin-6-deficient mice after partial hepatectomy. *Hepatology* 1999;**29**:403–411
40. Taub R. Liver regeneration: from myth to mechanism. *Nat Rev Mol Cell Biol* 2004;**5**:836–847
41. Brenner C, Galluzzi L, Kepp O, Kroemer G. Decoding cell death signals in liver inflammation. *J Hepatol* 2013;**59**:583–594

42. Schmidt SC, Hamann S, Langrehr JM, Höflich C, Mittler J, Jacob D *et al.* Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. *J Hepatobiliary Pancreat Surg* 2007;**14**:484–492
43. Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am J Physiol Gastrointest Liver Physiol* 2003;**284**:G15–G26
44. Ortmayr G, Brunnthaler L, Pereyra D, Huber H, Santol J, Rumpf B *et al.* Immunological aspects of AXL/GAS-6 in the context of human liver regeneration. *Hepatol Commun* 2022;**6**: 576–592
45. Eshkenazy R, Dreznik Y, Lahat E, Zakai BB, Zendel A, Ariche A. Small for size liver remnant following resection: prevention and management. *Hepatobiliary Surg Nutr* 2014;**3**:303–312
46. Martins PN, Theruvath TP, Neuhaus P. Rodent models of partial hepatectomies. *Liver Int* 2008;**28**:3–11
47. Bockamp E, Sprengel R, Eshkind L, Lehmann T, Braun JM, Emmrich F *et al.* Conditional transgenic mouse models: from the basics to genome-wide sets of knockouts and current studies of tissue regeneration. *Regen Med* 2008;**3**:217–235
48. Yokoyama Y, Schwacha MG, Samy TS, Bland KI, Chaudry IH. Gender dimorphism in immune responses following trauma and hemorrhage. *Immunol Res* 2002;**26**:63–76
49. Tsugawa Y, Natori M, Handa H, Imai T. Estradiol accelerates liver regeneration through estrogen receptor α. *Clin Exp Gastroenterol* 2019;**12**:331–336
50. Ku G DlC, Aizpuru M, Hackl H, Ubl DS, Habermann EB, Pery R *et al.* Hepatocellular carcinoma as predominant cancer subgroup accounting for sex differences in post-hepatectomy liver failure, morbidity and mortality. *HPB (Oxford)* 2022;**24**: 1453–1463
51. Timchenko NA. Aging and liver regeneration. *Trends Endocrinol Metab* 2009;**20**:171–176
52. Furrer K, Rickenbacher A, Tian Y, Jochum W, Bittermann AG, Käch A *et al.* Serotonin reverts age-related capillarization and failure of regeneration in the liver through a VEGF-dependent pathway. *Proc Natl Acad Sci USA* 2011;**108**:2945–2950
53. Kaibori M, Inoue T, Sakakura Y, Oda M, Nagahama T, Kwon AH *et al.* Impairment of activation of hepatocyte growth factor precursor into its mature form in rats with liver cirrhosis. *J Surg Res* 2002;**106**:108–114
54. 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
55. Bucher NL. Insulin, glucagon, and the liver. *Adv Enzyme Regul* 1976;**15**:221–230
56. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut* 2005;**54**:289–296
57. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med* 1994;**331**:1547–1552
58. 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
59. 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
60. Mehta NN, Ravikumar R, Coldham CA, Buckels JA, Hubscher SG, Bramhall SR *et al.* Effect of preoperative chemotherapy on liver resection for colorectal liver metastases. *Eur J Surg Oncol* 2008;**34**:782–786
61. 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
62. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival–a European single center experience. *Eur J Surg Oncol* 2005;**31**: 986–993
63. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC *et al.* Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;**111**:1018–1022
64. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR. Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. *Am J Surg* 1992;**163**: 515–518
65. Yamanaka N, Okamoto E, Kawamura E, Kato T, Oriyama T, Fujimoto J *et al.* Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. *Hepatology* 1993;**18**: 79–85
66. Cherqui D, Benoist S, Malassagne B, Humeres R, Rodriguez V, Fagniez PL. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. *Arch Surg* 2000;**135**:302–308
67. Makino H, Shimizu H, Ito H, Kimura F, Ambiru S, Togawa A *et al.* Changes in growth factor and cytokine expression in biliary obstructed rat liver and their relationship with delayed liver regeneration after partial hepatectomy. *World J Gastroenterol* 2006;**12**:2053–2059
68. Otao R, Beppu T, Isiko T, Mima K, Okabe H, Hayashi H *et al.* External biliary drainage and liver regeneration after major hepatectomy. *Br J Surg* 2012;**99**:1569–1574
69. Koelfat KVK, van Mierlo KMC, Lodewick TM, Bloemen JG, van der Kroft G, Amygdalos I *et al.* Bile salt and FGF19 signaling in the early phase of human liver regeneration. *Hepatol Commun* 2021;**5**:1400–1411
70. 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
71. Golse N, Joly F, Combari P, Lewin M, Nicolas Q, Audebert C *et al.* Predicting the risk of post-hepatectomy portal hypertension using a digital twin: a clinical proof of concept. *J Hepatol* 2021; **74**:661–669
72. 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
73. Bismuth H, Majno PE. Hepatobiliary surgery. *J Hepatol* 2000;**32**: 208–224
74. Li C, Mi K, Wen TF, Yan LN, Li B. Safety of patients with a graft to body weight ratio less than 0.8 per cent in living donor liver transplantation using right hepatic lobe without middle hepatic vein. *Hepatogastroenterology* 2012;**59**:469–472
75. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003;**138**:1198–1206; discussion 206

76. Fagenson AM, Gleeson EM, Nabi F, Lau KN, Pitt HA. When does a Pringle maneuver cause harm? *HPB (Oxford)* 2021;**23**:587–594
77. Fujii Y, Shimada H, Endo I, Morioka D, Nagano Y, Miura Y *et al.* Risk factors of posthepatectomy liver failure after portal vein embolization. *J Hepatobiliary Pancreat Surg* 2003;**10**:226–232
78. Savlid M, Strand AH, Jansson A, Agustsson T, Söderdahl G, Lundell L *et al.* Transection of the liver parenchyma with an ultrasound dissector or a stapler device: results of a randomized clinical study. *World J Surg* 2013;**37**:799–805
79. Schwarz C, Klaus DA, Tudor B, Fleischmann E, Wekerle T, Roth G *et al.* Transection speed and impact on perioperative inflammatory response—a randomized controlled trial comparing stapler hepatectomy and CUSA resection. *PloS One* 2015;**10**:e0140314-e
80. Pan Y, Xia S, Cai J, Chen K, Cai X. Efficacy of laparoscopic hepatectomy versus open surgery for hepatocellular carcinoma with cirrhosis: a meta-analysis of case-matched studies. *Front Oncol* 2021;**11**:652272
81. Wu X, Huang Z, Lau WY, Li W, Lin P, Zhang L *et al.* Perioperative and long-term outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with well-preserved liver function and cirrhotic background: a propensity score matching study. *Surg Endosc* 2019;**33**:206–215
82. Casellas-Robert M, Lim C, Lopez-Ben S, Llado L, Salloum C, Codina-Font J *et al.* Laparoscopic liver resection for hepatocellular carcinoma in Child-Pugh A patients with and without portal hypertension: a multicentre study. *World J Surg* 2020;**44**:3915–3922
83. Cipriani F, Fantini C, Ratti F, Lauro R, Tranchart H, Halls M *et al.* Laparoscopic liver resections for hepatocellular carcinoma. Can we extend the surgical indication in cirrhotic patients? *Surg Endosc* 2018;**32**:617–626
84. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? *Dig Surg* 2012;**29**:6–17
85. Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T *et al.* Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 1999;**188**:304–309
86. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH *et al.* Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;**7**:325–330
87. Van Thiel DH, Hagler NG, Schade RR, Skolnick ML, Heyl AP, Rosenblum E *et al.* In vivo hepatic volume determination using sonography and computed tomography. Validation and a comparison of the two techniques. *Gastroenterology* 1985;**88**:1812–1817
88. Ribero D, Amisano M, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A *et al.* Measured versus estimated total liver volume to preoperatively assess the adequacy of the future liver remnant: which method should we use? *Ann Surg* 2013;**258**:801–806, discussion 6–7
89. Ribero D, Chun YS, Vauthey JN. Standardized liver volumetry for portal vein embolization. *Semin Intervent Radiol* 2008;**25**:104–109
90. Olthof PB, van Dam R, Jovine E, Campos RR, de Santibanes E, Oldhafer K *et al.* Accuracy of estimated total liver volume formulas before liver resection. *Surgery* 2019;**166**:247–253
91. Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O *et al.* Remnant liver volume to body weight ratio > or = 0.5 per cent: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg* 2007;**204**:22–33
92. Pulitano C, Crawford M, Joseph D, Aldrighetti L, Sandroussi C. Preoperative assessment of postoperative liver function: the importance of residual liver volume. *J Surg Oncol* 2014;**110**:445–450
93. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;**13**:1271–1280
94. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ *et al.* Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 2009;**250**:540–548
95. Takahashi T, Togo S, Tanaka K, Endo I, Fujii Y, Shimada H. Safe and permissible limits of hepatectomy in obstructive jaundice patients. *World J Surg* 2004;**28**:475–481
96. Olthof PB, Coelen RJS, Bennink RJ, Heger M, Lam MF, Besselink MG *et al.* (99 m)Tc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma. *HPB (Oxford)* 2017;**19**:850–858
97. Suda K, Ohtsuka M, Ambiru S, Kimura F, Shimizu H, Yoshidome H *et al.* Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies. *Am J Surg* 2009;**197**:752–758
98. Tu R, Xia LP, Yu AL, Wu L. Assessment of hepatic functional reserve by cirrhosis grading and liver volume measurement using CT. *World J Gastroenterol* 2007;**13**:3956–3961
99. Yoshino K, Yoh T, Taura K, Seo S, Ciria R, Briceno-Delgado J. A systematic review of prediction models for post-hepatectomy liver failure in patients undergoing liver surgery. *HPB (Oxford)* 2021;**23**:1311–1320
100. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? *Digest Surg* 2012;**29**:6–17
101. Rassam F, Olthof PB, van Lienden KP, Bennink RJ, Erdmann JI, Swijnenburg RJ *et al.* Comparison of functional and volumetric increase of the future remnant liver and postoperative outcomes after portal vein embolization and complete or partial associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). *Ann Transl Med* 2020;**8**:436
102. Fagenson AM, Gleeson EM, Pitt HA, Lau KN. Albumin-bilirubin score vs model for end-stage liver disease in predicting post-hepatectomy outcomes. *J Am Coll Surg* 2020;**230**:637–645
103. Wong JSW, Wong GLH, Chan AWH, Wong VWS, Cheung YS, Chong CN *et al.* Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. *Ann Surg* 2013;**257**:922–928
104. Grainger SL, Keeling PWN, Brown IMH, Marigold JH, Thompson RPH. Clearance and non-invasive determination of the hepatic extraction of indocyanine green in baboons and man. *Clin Sci* 1983;**64**:207–212
105. Ekman M, Fjalling M, Friman S, Carlson S, Volkmann R. Liver uptake function measured by IODIDA clearance rate in liver transplant patients and healthy volunteers. *Nucl Med Commun* 1996;**17**:235–242
106. Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB (Oxford)* 2010;**12**:139–146
107. Haegele S, Reiter S, Wanek D, Offensperger F, Pereyra D, Stremitzer S *et al.* Perioperative non-invasive indocyanine

green-clearance testing to predict postoperative outcome after liver resection. *PLoS ONE* 2016;**11**:e0165481
108. Rassam F, Olthof PB, Richardson H, van Gulik TM, Bennink RJ. Practical guidelines for the use of technetium-99 m mebrofenin hepatobiliary scintigraphy in the quantitative assessment of liver function. *Nucl Med Commun* 2019;**40**:297–307
109. Kubota Y, Kitagawa S, Inoue K, Hakawa SK, Kojima M, Tanaka Y. Hepatic functional scintigraphic imaging with tc-99 m galactosyl serum-albumin. *Hepato-Gastroenterol* 1993;**40**:32–36
110. Wang Q, Kesen S, Liljeroth M, Nilsson H, Zhao Y, Sparrelid E *et al.* Quantitative evaluation of liver function with gadoxetic acid enhanced MRI: comparison among signal intensity-, T1-relaxometry-, and dynamic-hepatocyte-specific-contrast-enhanced MRI- derived parameters. *Scand J Gastroenterol* 2022;**57**:705–712
111. Notake T, Shimizu A, Kubota K, Ikehara T, Hayashi H, Yasukawa K *et al.* Hepatocellular uptake index obtained with gadoxetate disodium-enhanced magnetic resonance imaging in the assessment future liver remnant function after major hepatectomy for biliary malignancy. *BJS Open* 2021;**5**:zraa048
112. Evans R, Taylor S, Janes S, Halligan S, Morton A, Navani N *et al.* Patient experience and perceived acceptability of whole-body magnetic resonance imaging for staging colorectal and lung cancer compared with current staging scans: a qualitative study. *BMJ Open* 2017;**7**:e016391
113. de Graaf W, van Lienden KP, Dinant S, Roelofs JJTH, Busch ORC, Gouma DJ *et al.* Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg* 2010;**14**:369–378
114. Gupta M, Choudhury PS, Singh S, Hazarika D. Liver functional volumetry by tc-99 m mebrofenin hepatobiliary scintigraphy before major liver resection: a game changer. *Indian J Nucl Med* 2018;**33**:277–283
115. Serenari M, Bonatti C, Zanoni L, Peta G, Tabacchi E, Cucchetti A *et al.* The role of hepatobiliary scintigraphy combined with spect/CT in predicting severity of liver failure before major hepatectomy: a single-center pilot study. *Updates Surg* 2021;**73**:197–208
116. Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. *J Hepato-Biliary-Pancreat Surg* 2007;**14**:159–166
117. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001;**88**:165–175
118. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J *et al.* Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 2008;**247**:49–57
119. 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
120. 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
121. Olthof PB, Aldrighetti L, Alikhanov R, Cescon M, Groot Koerkamp B, Jarnagin WR *et al.* Portal vein embolization is associated with reduced liver failure and mortality in high-risk resections for perihilar cholangiocarcinoma. *Ann Surg Oncol* 2020;**27**:2311–2318
122. Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, Yamaguchi J *et al.* The predictive value of indocyanine green clearance in future liver remnant for posthepatectomy liver failure following hepatectomy with extrahepatic bile duct resection. *World J Surg* 2016;**40**:1440–1447
123. Franken LC, Rassam F, van Lienden KP, Bennink RJ, Besselink MG, Busch OR *et al.* Effect of structured use of preoperative portal vein embolization on outcomes after liver resection of perihilar cholangiocarcinoma. *BJS Open* 2020;**4**:449–455
124. Omichi K, Yamashita S, Cloyd JM, Shindoh J, Mizuno T, Chun YS *et al.* Portal vein embolization reduces postoperative hepatic insufficiency associated with postchemotherapy hepatic atrophy. *J Gastrointest Surg* 2018;**22**:60–67
125. Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, Lemoine A *et al.* Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann Surg* 2000;**232**:665–672
126. Azoulay D, Castaing D, Smail A, Adam R, Cailliez V, Laurent A *et al.* Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg* 2000;**231**:480–486
127. de Baere T, Roche A, Elias D, Lasser P, Lagrange C, Bousson V. Preoperative portal vein embolization for extension of hepatectomy indications. *Hepatology* 1996;**24**:1386–1391
128. Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH *et al.* Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg* 2013;**100**:1777–1783
129. Leung U, Simpson AL, Araujo RL, Gonen M, McAuliffe C, Miga MI *et al.* Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. *J Am Coll Surg* 2014;**219**:620–630
130. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg* 2000;**232**:777–785
131. Jaeck D, Bachellier P, Nakano H, Oussoultzoglou E, Weber JC, Wolf P *et al.* One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. *Am J Surg* 2003;**185**:221–229
132. 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
133. Schnitzbauer AA. A comparison of pitfalls after ALPPS stage 1 or portal vein embolization in small-for-size setting hepatectomies. *Visc Med* 2017;**33**:435–441
134. Sandstrom P, Rosok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G *et al.* ALPPS Improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a Scandinavian multicenter randomized controlled trial (LIGRO Trial). *Ann Surg* 2018;**267**:833–840
135. Schadde E, Raptis DA, Schnitzbauer AA, Ardiles V, Tschuor C, Lesurtel M *et al.* Prediction of mortality after ALPPS stage-1: an analysis of 320 patients from the international ALPPS registry. *Ann Surg* 2015;**262**:780–785, discussion 5–6
136. Huiskens J, Schadde E, Lang H, Malago M, Petrowsky H, de Santibanes E *et al.* Avoiding postoperative mortality after ALPPS-development of a tumor-specific risk score for colorectal liver metastases. *HPB (Oxford)* 2019;**21**:898–905
137. Ulmer TF, de Jong C, Andert A, Bruners P, Heidenhain CM, Schoening W *et al.* ALPPS procedure in insufficient

hypertrophy after portal vein embolization (PVE). *World J Surg* 2017;**41**:250–257
138. Sparrelid E, Gilg S, Brismar TB, Lundell L, Isaksson B. Rescue ALPPS is efficient and safe after failed portal vein occlusion in patients with colorectal liver metastases. *Langenbecks Arch Surg* 2017;**402**:69–75
139. Schadde E. Combined portal vein and hepatic vein embolization-finally the platinum procedure of regenerative liver surgery? *Hepatobiliary Surg Nutr* 2020;**9**:92–94
140. Petrowsky H, Linecker M, Raptis DA, Kuemmerli C, Fritsch R, Kirimker OE *et al.* First long-term oncologic results of the ALPPS procedure in a large cohort of patients with colorectal liver metastases. *Ann Surg* 2020;**272**:793–800
141. Guiu B, Chevallier P, Denys A, Delhom E, Pierredon-Foulongne MA, Rouanet P *et al.* Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. *Eur Radiol* 2016;**26**: 4259–4267
142. Laurent C, Fernandez B, Marichez A, Adam JP, Papadopoulos P, Lapuyade B *et al.* Radiological simultaneous portohepatic vein embolization (RASPE) before major hepatectomy: a better way to optimize liver hypertrophy compared to portal vein embolization. *Ann Surg* 2020;**272**:199–205
143. Kobayashi K, Yamaguchi T, Denys A, Perron L, Halkic N, Demartines N *et al.* Liver venous deprivation compared to portal vein embolization to induce hypertrophy of the future liver remnant before major hepatectomy: a single center experience. *Surgery* 2020;**167**:917–923
144. Panaro F, Giannone F, Riviere B, Sgarbura O, Cusumano C, Deshayes E *et al.* Perioperative impact of liver venous deprivation compared with portal venous embolization in patients undergoing right hepatectomy: preliminary results from the pioneer center. *Hepatobiliary Surg Nutr* 2019;**8**:329–337
145. Le Roy B, Gallon A, Cauchy F, Pereira B, Gagniere J, Lambert C *et al.* Combined biembolization induces higher hypertrophy than portal vein embolization before major liver resection. *HPB (Oxford)* 2020;**22**:298–305
146. Hocquelet A, Sotiriadis C, Duran R, Guiu B, Yamaguchi T, Halkic N *et al.* Preoperative portal vein embolization alone with biliary drainage compared to a combination of simultaneous portal vein, right hepatic vein embolization and biliary drainage in Klatskin tumor. *Cardiovasc Intervent Radiol* 2018;**41**:1885–1891
147. Heil J, Schadde E. Simultaneous portal and hepatic vein embolization before major liver resection. *Langenbecks Arch Surg* 2021;**406**:1295–1305
148. Pringle JHV. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg* 1908;**48**:541–549
149. Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg* 2006;**93**: 685–689
150. Lee KF, Cheung YS, Wong J, Chong CC, Wong JS, Lai PB. Randomized clinical trial of open hepatectomy with or without intermittent Pringle manoeuvre. *Br J Surg* 2012;**99**: 1203–1209
151. Zhai Y, Busuttil RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant* 2011;**11**:1563–1569
152. Teoh NC, Farrell GC. Hepatic ischemia reperfusion injury: pathogenic mechanisms and basis for hepatoprotection. *J Gastroenterol Hepatol* 2003;**18**:891–902
153. Badia JM, Ayton CL, Evans TJ, Carpenter AJ, Nawfal G, Kinderman H *et al.* Systemic cytokine response to hepatic resections under total vascular exclusion. *Eur J Surg* 1998;**164**: 185–190
154. Kim YI, Song KE, Ryeon HK, Hwang YJ, Yun YK, Lee JW *et al.* Enhanced inflammatory cytokine production at ischemia/ reperfusion in human liver resection. *Hepatogastroenterology* 2002;**49**:1077–1082
155. Dello SAWG, Reisinger KW, van Dam RM, Bemelmans MHA, van Kuppevelt TH, van den Broek MAJ *et al.* Total intermittent Pringle maneuver during liver resection can induce intestinal epithelial cell damage and endotoxemia. *Plos One* 2012;**7**:e30539
156. Kambakamba P, Linecker M, Schneider M, Kron P, Limani P, Tschuor C *et al.* Novel benefits of remote ischemic preconditioning through VEGF-dependent protection from resection-induced liver failure in the mouse. *Ann Surg* 2018; **268**:885–893
157. O'Neill S, Leuschner S, McNally SJ, Garden OJ, Wigmore SJ, Harrison EM. Meta-analysis of ischaemic preconditioning for liver resections. *Br J Surg* 2013;**100**:1689–1700
158. Belghiti J, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F *et al.* Continuous versus intermittent portal triad clamping for liver resection—a controlled study. *Ann Surg* 1999;**229**:369–375
159. Fagenson AM, Gleeson EM, Nabi F, Lau KN, Pitt HA. When does a Pringle maneuver cause harm? *HPB (Oxford)* 2021;**23**:587–594
160. Sanjay P, Ong I, Bartlett A, Powell JJ, Wigmore SJ. Meta-analysis of intermittent Pringle manoeuvre versus no Pringle manoeuvre in elective liver surgery. *Anz J Surg* 2013;**83**:719–723
161. Ni JS, Lau WY, Yang Y, Pan ZY, Wang ZG, Liu H *et al.* A prospective randomized controlled trial to compare Pringle manoeuvre with hemi-hepatic vascular inflow occlusion in liver resection for hepatocellular carcinoma with cirrhosis. *J Gastrointest Surg* 2013;**17**:1414–1421
162. Ishizuka M, Kubota K, Kita J, Shimoda M, Kato M, Sawada T. Duration of hepatic vascular inflow clamping and survival after liver resection for hepatocellular carcinoma. *Br J Surg* 2011;**98**:1284–1290
163. Huang Y, Liao A, Pu X, Yang J, Lv T, Yan L *et al.* A randomized controlled trial of effect of 15- or 25-min intermittent Pringle maneuver on hepatectomy for hepatocellular carcinoma. *Surgery* 2022;**171**:1596–1604
164. Melendez J, Ferri E, Zwillman M, Fischer M, DeMatteo R, Leung D *et al.* Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. *J Am Coll Surg* 2001; **192**:47–53
165. Zimmitti G, Vauthey JN, Shindoh J, Tzeng CW, Roses RE, Ribero D *et al.* Systematic use of an intraoperative air leak test at the time of major liver resection reduces the rate of postoperative biliary complications. *J Am Coll Surg* 2013;**217**: 1028–1037
166. Ma JY, Li XF, Yan ZL, Hasan MM, Wang K, Wang Y *et al.* Randomized controlled trial of hepatic portal reocclusion as a new option for detecting bile leakage during hepatic resection. *Dig Surg* 2017;**34**:328–334
167. Li J, Malago M, Sotiropoulos GC, Lang H, Schaffer R, Paul A *et al.* Intraoperative application of "white test" to reduce postoperative bile leak after major liver resection: results of a prospective cohort study in 137 patients. *Langenbecks Arch Surg* 2009;**394**:1019–1024
168. Christ B, Collatz M, Dahmen U, Herrmann KH, Hopfl S, Konig M *et al.* Hepatectomy-induced alterations in hepatic perfusion and function—toward multi-scale computational modeling

for a better prediction of post-hepatectomy liver function. *Front Physiol* 2021;**12**:733868
169. Eipel C, Abshagen K, Ritter J, Cantre D, Menger MD, Vollmar B. Splenectomy improves survival by increasing arterial blood supply in a rat model of reduced-size liver. *Transpl Int* 2010; **23**:998–1007
170. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl* 2003;**9**:S36–S41
171. Wang H, Ikegami T, Harada N, Yoshizumi T, Soejima Y, Uchiyama H *et al.* Optimal changes in portal hemodynamics induced by splenectomy during living donor liver transplantation. *Surg Today* 2015;**45**:979–985
172. Nagao Y, Akahoshi T, Kamori M, Uehara H, Hashimoto N, Kinjo N *et al.* Liver regeneration is promoted by increasing serotonin content in rat liver with secondary biliary cirrhosis. *Hepatol Res* 2011;**41**:784–794
173. Troisi R, Hoste E, Van Langenhove P, Decruyenaere J, Voet D, Hesse UJ *et al.* Modulation of liver graft hemodynamics by partial ablation of the splenic circuit: a way to increase hepatic artery flow? *Transplant Proc* 2001;**33**:1445–1446
174. Rhaiem R, Piardi T, Chetboun M, Pessaux P, Lestra T, Memeo R *et al.* Portal inflow modulation by somatostatin after Major liver resection: a pilot study. *Ann Surg*. 2018;**267**:e101–e103
175. Hammond JS, Godtliebsen F, Steigen S, Guha IN, Wyatt J, Revhaug A *et al.* The effects of terlipressin and direct portacaval shunting on liver hemodynamics following 80 per cent hepatectomy in the pig. *Clin Sci (Lond)* 2019;**133**:153–166
176. Jo HS, Park HJ, Choi YY, Seok JI, Han JH, Yoon YI *et al.* Portal modulation effects of terlipressin on liver regeneration and survival in a porcine model subjected to 90 per cent hepatectomy. *Am J Transl Res* 2021;**13**:5880–5891
177. Hessheimer AJ, Escobar B, Munoz J, Flores E, Gracia-Sancho J, Taura P *et al.* Somatostatin therapy protects porcine livers in small-for-size liver transplantation. *Am J Transplant* 2014;**14**: 1806–1816
178. Kohler A, Perrodin S, De Gottardi A, Candinas D, Beldi G. Effectiveness of terlipressin for prevention of complications after major liver resection—a randomized placebo-controlled trial. *HPB (Oxford)* 2020;**22**:884–891
179. Jegatheeswaran S, Siriwardena AK. Experimental and clinical evidence for modification of hepatic ischaemia-reperfusion injury by *N*-acetylcysteine during major liver surgery. *HPB (Oxford)* 2011;**13**:71–78
180. Grendar J, Ouellet JF, McKay A, Sutherland FR, Bathe OF, Ball CG *et al.* Effect of N-acetylcysteine on liver recovery after resection: a randomized clinical trial. *J Surg Oncol* 2016;**114**: 446–450
181. Robinson SM, Saif R, Sen G, French JJ, Jaques BC, Charnley RM *et al.* N-acetylcysteine administration does not improve patient outcome after liver resection. *HPB (Oxford)* 2013;**15**:457–462
182. Schmidt SC, Hamann S, Langrehr JM, Hoflich C, Mittler J, Jacob D *et al.* Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. *J Hepatobiliary Pancreat Surg* 2007;**14**:484–492
183. Hayashi Y, Takayama T, Yamazaki S, Moriguchi M, Ohkubo T, Nakayama H *et al.* Validation of perioperative steroids administration in liver resection: a randomized controlled trial. *Ann Surg* 2011;**253**:50–55
184. Hasegawa Y, Nitta H, Takahara T, Katagiri H, Kanno S, Umemura A *et al.* Glucocorticoid use and ischemia-reperfusion injury in laparoscopic liver resection: randomized controlled trial. *Ann Gastroenterol Surg* 2020;**4**: 76–83
185. Steinthorsdottir KJ, Awada HN, Schultz NA, Larsen PN, Hillingso JG, Jans O *et al.* Preoperative high-dose glucocorticoids for early recovery after liver resection: randomized double-blinded trial. *BJS Open* 2021;**5**:zrab063
186. Richardson AJ, Laurence JM, Lam VW. Use of pre-operative steroids in liver resection: a systematic review and meta-analysis. *HPB (Oxford)* 2014;**16**:12–19
187. European Association for the Study of the Liver *et al.* EASL clinical practical guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017;**66**:1047–1081
188. Lafaro K, Buettner S, Maqsood H, Wagner D, Bagante F, Spolverato G *et al.* Defining post hepatectomy liver insufficiency: where do we stand? *J Gastrointest Surg* 2015;**19**: 2079–2092
189. Soreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) —recent advances in prevention and clinical management. *Eur J Surg Oncol* 2021;**47**:216–224
190. Dasari BV, Rahman R, Khan S, Bennett D, Hodson J, Isaac J *et al.* Safety and feasibility of an enhanced recovery pathway after a liver resection: prospective cohort study. *HPB (Oxford)* 2015;**17**: 700–706
191. Garwood RA, Sawyer RG, Thompson L, Adams RB. Infectious complications after hepatic resection. *Am Surg* 2004;**70**: 787–792
192. Murtha-Lemekhova A, Fuchs J, Teroerde M, Chiriac U, Klotz R, Hornuss D *et al.* Routine postoperative antibiotic prophylaxis offers no benefit after hepatectomy-a systematic review and meta-analysis. *Antibiotics (Basel)* 2022;**11**:649
193. Saadat LV, Brajcich BC, Liu Y, Ko C, D'Angelica MI. Defining the risk of liver failure after minor hepatectomy: a NSQIP analysis of 7029 patients. *HPB (Oxford)* 2021;**23**:551–559
194. Haussinger D, Dhiman RK, Felipo V, Gorg B, Jalan R, Kircheis G *et al.* Hepatic encephalopathy. *Nat Rev Dis Primers* 2022;**8**:43
195. Watanabe Y, Tsuchiya A, Seino S, Kawata Y, Kojima Y, Ikarashi S *et al.* Mesenchymal stem cells and induced bone marrow-derived macrophages synergistically improve liver fibrosis in mice. *Stem Cells Transl Med* 2019;**8**:271–284
196. Lei Z, Cheng N, Si A, Yang P, Guo G, Ma W *et al.* A novel nomogram for predicting postoperative liver failure after Major hepatectomy for hepatocellular carcinoma. *Front Oncol* 2022;**12**:817895
197. Iseki M, Mizuma M, Wakao S, Kushida Y, Kudo K, Fukase M *et al.* The evaluation of the safety and efficacy of intravenously administered allogeneic multilineage-differentiating stress-enduring cells in a swine hepatectomy model. *Surg Today* 2021;**51**:634–650
198. Wang JL, Ding HR, Pan CY, Shi XL, Ren HZ. Mesenchymal stem cells ameliorate lipid metabolism through reducing mitochondrial damage of hepatocytes in the treatment of post-hepatectomy liver failure. *Cell Death Dis* 2021;**12**:111
199. Watanabe Y, Tsuchiya A, Terai S. The development of mesenchymal stem cell therapy in the present, and the perspective of cell-free therapy in the future. *Clin Mol Hepatol* 2021;**27**:70–80
200. Nevens F, Laleman W. Artificial liver support devices as treatment option for liver failure. *Best Pract Res Clin Gastroenterol* 2012;**26**:17–26
201. Stange J, Ramlow W, Mitzner S, Schmidt R, Klinkmann H. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. *Artif Organs* 1993;**17**: 809–813

202. Stange J, Mitzner SR, Risler T, Erley CM, Lauchart W, Goehl H *et al.* Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. *Artif Organs* 1999;**23**:319–330
203. Catalina MV, Barrio J, Anaya F, Salcedo M, Rincon D, Clemente G *et al.* Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. *Liver Int* 2003;**23**:39–43
204. Sen S, Mookerjee RP, Cheshire LM, Davies NA, Williams R, Jalan R. Albumin dialysis reduces portal pressure acutely in patients with severe alcoholic hepatitis. *J Hepatol* 2005;**43**:142–148
205. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M *et al.* Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology* 2013;**57**:1153–1162
206. Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B *et al.* Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. *Ann Intern Med* 2013;**159**:522–531
207. Tandon R, Froghi S. Artificial liver support systems. *J Gastroenterol Hepatol* 2021;**36**:1164–1179
208. Wallon G, Guth C, Guichon C, Thevenon S, Gazon M, Viale JP *et al.* Extracorporeal albumin dialysis in liver failure with MARS and SPAD: a randomized crossover trial. *Blood Purif* 2022;**51**:243–250
209. Peszynski P, Klammt S, Peters E, Mitzner S, Stange J, Schmidt R. Albumin dialysis: single pass vs. recirculation (MARS). *Liver* 2002;**22**:40–42
210. 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
211. Gilg S, Sparrelid E, Saraste L, Nowak G, Wahlin S, Stromberg C *et al.* The molecular adsorbent recirculating system in posthepatectomy liver failure: results from a prospective phase I study. *Hepatol Commun* 2018;**2**:445–454
212. Sparrelid E, Gilg S, van Gulik TM. Systematic review of MARS treatment in post-hepatectomy liver failure. *HPB (Oxford)* 2020;**22**:950–960
213. Demetriou AA, Brown RS, Jr., Busuttil RW, Fair J, McGuire BM, Rosenthal P *et al.* Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg*. 2004;**239**:660–667; discussion 7–70
214. van de Kerkhove MP, Poyck PP, Deurholt T, Hoekstra R, Chamuleau RA, van Gulik TM. Liver support therapy: an overview of the AMC-bioartificial liver research. *Dig Surg* 2005;**22**:254–264
215. He YT, Qi YN, Zhang BQ, Li JB, Bao J. Bioartificial liver support systems for acute liver failure: a systematic review and meta-analysis of the clinical and preclinical literature. *World J Gastroenterol* 2019;**25**:3634–3648
216. 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
217. Thorsen T, Solheim JM, Labori KJ, Line PD, Aandahl EM. Liver transplantation as a lifesaving procedure for posthepatectomy liver failure and iatrogenic liver injuries. *Langenbecks Arch Surg* 2019;**404**:301–308
218. Sparrelid E, Thorsen T, Sauter C, Jorns C, Stal P, Nordin A *et al.* Liver transplantation in patients with post-hepatectomy liver failure—a northern European multicenter cohort study. *HPB (Oxford)* 2021;**24**:1138–1144
219. Skrzypczyk C, Truant S, Duhamel A, Langlois C, Boleslawski E, Koriche D *et al.* Relevance of the ISGLS definition of posthepatectomy liver failure in early prediction of poor outcome after liver resection: study on 680 hepatectomies. *Ann Surg* 2014;**260**:865–870; discussion 70
220. Harrison EM, O'Neill S, Wigmore SJ, James Garden O. Comparison of binary predictive scoring systems of posthepatectomy liver failure. *Ann Surg* 2017;**265**:e56–e57
221. Skrzypczyk C, Truant S, Duhamel A, Langlois C, Boleslawski E, Hebbar M *et al.* Comparison of binary predictive scoring systems of posthepatectomy liver failure: a response. *Ann Surg* 2017;**265**:e57–e58