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Current evidence on posthepatectomy liver failure: comprehensive review

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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

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.*[2,19] 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.*[2,19]
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.*[2,19] 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
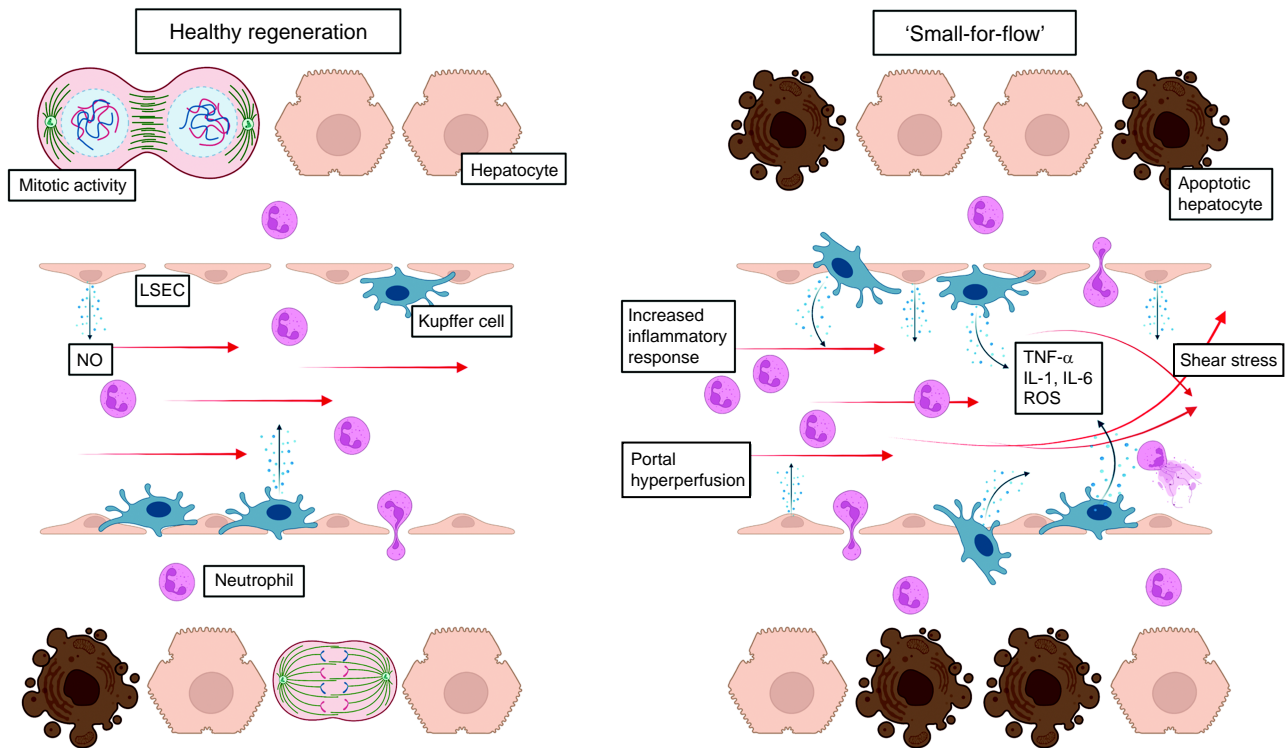
Fig. 1 Schematic overview of normal and dysfunctional liver regeneration

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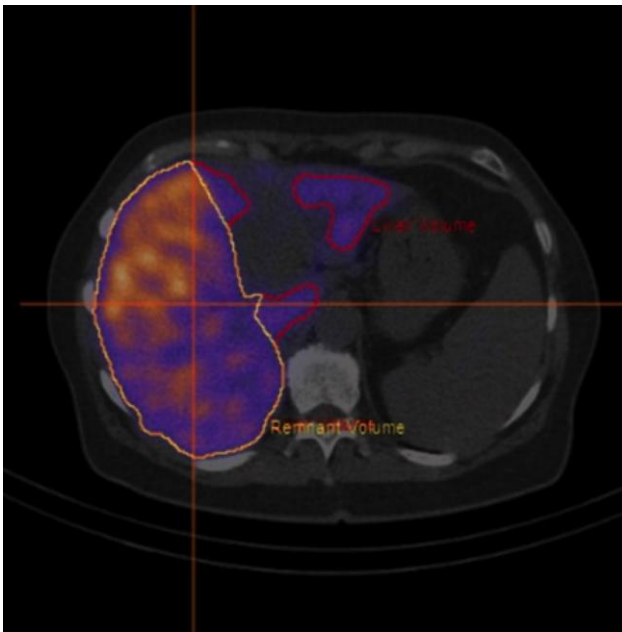
Fig. 2 Regional distribution of liver function assessed with hepatobiliary scintigraphy

[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
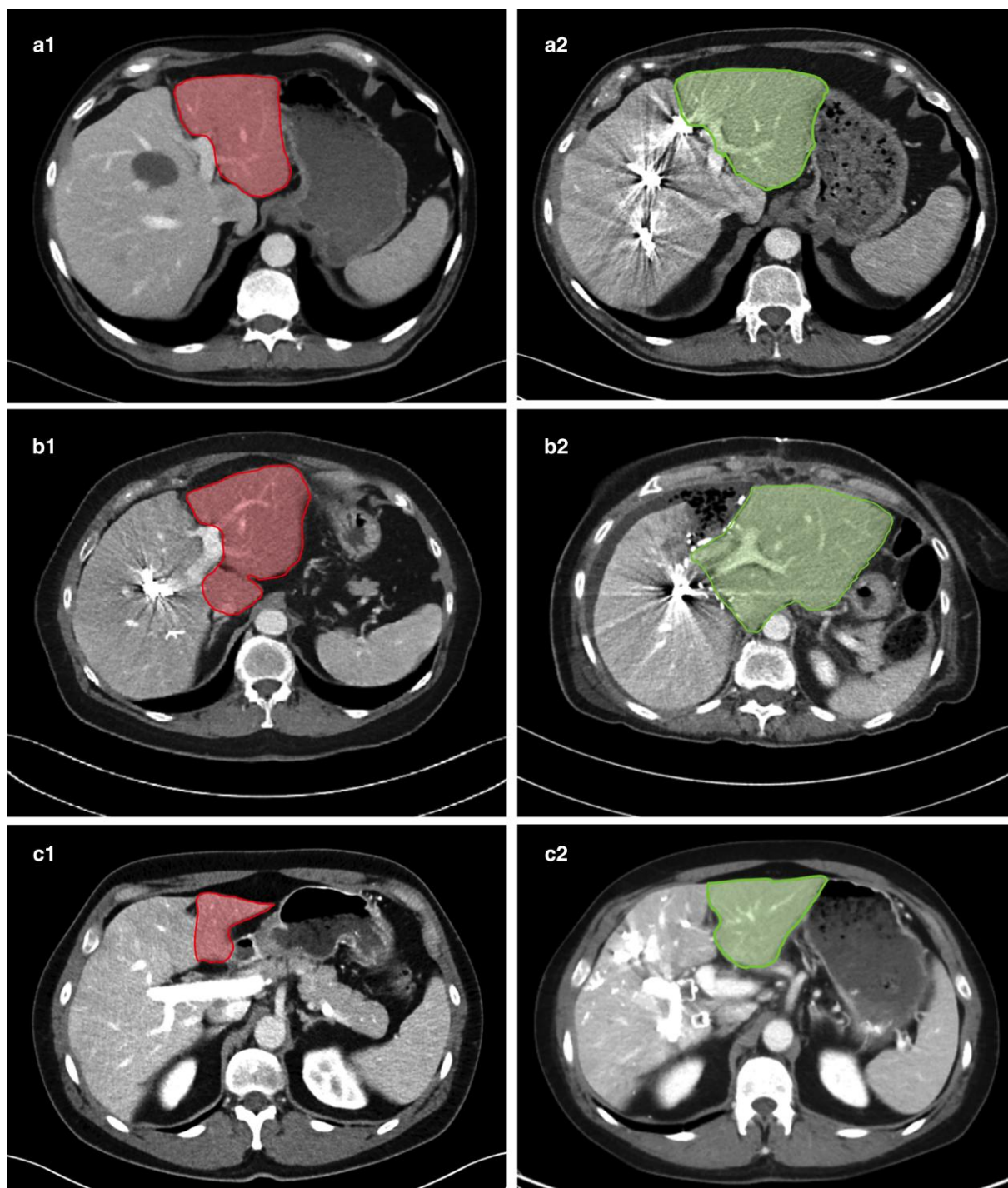
Fig. 3 Methods to increase future liver remnant size

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 radicals 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.

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Data availability

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

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