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REVIEW ARTICLE

Defining Post Hepatectomy Liver Insufficiency: Where do We stand?

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Abstract
Background Post-hepatectomy liver failure (PHLF) is a major source of morbidity and mortality in patients undergoing liver resection. The aim of this review is to summarize the recent literature available on PHLF including its definition, predictive factors, preoperative risk assessment, severity grading, preventative measures, and management strategies.
Methods A systematic literature search was carried out with the search engines PubMed, Medline, and Cochrane Database using the keywords related to "liver failure", "posthepatectomy", and "hepatic resection".
Results Liver resection is a curative treatment of liver tumors. However, it leads to concurrent death and regeneration of the remaining hepatocytes. Factors related to the patient, liver parenchyma and the extent of surgery can inhibit regeneration leading to PHLF.
Conclusion Given its resistance to treatment and the high postoperative mortality associated with PHLF, great effort has been put in to both accurately identify patients at high risk and to develop strategies that can help prevent its occurrence.

Keywords Hepatectomy · Complications · Liver failure · Risk models · Surgery/mortality

Introduction

Liver resection remains the mainstay of treatment for both primary and secondary liver tumors. Advances in operative techniques, perioperative care, and patients selection have resulted in an increase in the number of patients who are amenable to surgical resection, as well as decreased the morbidity and mortality associated with liver surgery.[1–3] However, one of the most serious complications following liver resection is the development of post-hepatectomy liver insufficiency/failure (PHLF), which can be a major cause of morbidity and mortality.[4–6] The reported incidence of PHLF varies between 0.7 and 34 % in the literature.[4,7–10] This wide range of incidence may be explained, in part, by the different definitions of PHLF, variability of the extent of hepatic resection (wedge resection vs. minor vs. major hepatectomy), as well as the diverse characteristics of the patients analysed.[4,11]

We herein review the risk factors associated with PHLF, as well as the different definitions and predication models reported in the literature. In addition, we highlight several proposed prevention and treatment strategies for PHLF.

Methods

A systematic literature search was carried out with the search engines PubMed, Medline, and Cochrane Database using the

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keywords related to "liver failure", "liver insufficiency", "post-hepatectomy", "morbidity", "mortality", and "hepatic resection". The resulting relevant English language studies were identified and reviewed.

Incidence

The incidence of PHLF varies between 0.7 and 34 % in the literature with most recent reports noting an incidence around 5–10 %.[4,7–10] The wide range of incidence may partially be explained by the lack of a uniform definition of PHLF.[4,11] There has been a decrease in incidence of PHLF over the past two decades likely due to improvements in surgical technique and perioperative care that have led to decreased mortality following hepatic resection. Mortality following partial hepatectomy in the past two decades still ranges from 0 to 6 %, however, and PHLF has been implicated as contributing to mortality in the majority of cases.[4,12,13]

Risk Factors for Post Hepatectomy Liver Failure

Identification of the risk factors for PHLF is critical to help identify patients most at risk, as well as to inform strategies aimed at decreasing the incidence and mortality associated with PHLF. Independent predictors of PHLF can be categorized into three main categories: patient- related, liver- related, and surgery/postop-related factors (Table 1).

Table 1 Risk factors for PHLF

Patient-related factors
Age (>65 years)
Male gender
Metabolic disorders
Preoperative chemotherapy
Sepsis
Malnutrition
ASA score
Liver- related factors
Grade of the tumour
Hepatitis
Portal venous pressure
Cirrhosis
Cholestasis
Surgery- related factors
Complex operations
Extent of resection
General surgical models
Large blood transfusion
Left hepatectomy
Duration of Pringle Maneuvre

Patient-Related Factors

Patient-related factors associated with PHLF include age, male gender, malnutrition, diabetes, and American Society of Anesthesiology (ASA) score. Some studies had implicated older age as a risk factor for PHLF; however, other studies have documented the safety of liver resection in the elderly. Animal models have suggested a loss of the liver's regenerative capacity, as well as impaired liver function with increased age.[14–17] In a study of 775 patients, Balzan et al. reported age over 65 years as an independent predictor of death in multivariate analysis.[18] In a subsequent study, Mullen et al. evaluated 1509 non-cirrhotic patients undergoing hepatectomy and found older age to be an independent predictor of morbidity as well as death from liver failure.[19] However, clinical data from several major centers have documented that hepatectomy can be performed with low morbidity in older patients. For example, in a study of 129 patients, Aldrighetti et al. reported that age >70 years did not correlated with an increased morbidity or mortality following partial liver resection.[20] In a separate study, while an increase in the incidence of systemic complications was noted among elderly patients following hepatectomy for hepatocellular carcinoma (HCC), Nanashima et al. failed to detect a difference in the incidence of hepatic failure.[21] Similarly, Kim et al. in a study of 279 patients undergoing both minor and major liver resections did not find any age-related differences in postoperative PHLF.[22]

Diabetes, either alone or in combination with metabolic syndrome, has also been associated with a greater risk of PHLF. Little et al. reported on 727 patients who underwent liver resection and demonstrated an increase in 30-day mortality among diabetic versus non-diabetic patients ($p<0.02$); in fact, 80 % of the deaths in this study were attributable to PHLF.[23] The association of diabetes with the risk of PHLF may be due to the important role insulin plays in the regulation of hepatocyte function and regeneration. Specifically, a lack of insulin has been noted to cause hepatic atrophy in animal models.[24] In one clinical study, Zarzavadjian Le Bian et al. reported that in the 30 (19.8 %) of the 151 patients undergoing right hepatectomy who had two or more metabolic disorders (diabetes mellitus, hypertension, dyslipidemia, or obesity) perioperative mortality was 30 %.[25] In a different study of 245 patients with well-preserved liver function undergoing liver resection for HCC, Huo et al. reported that diabetes was an independent prognostic factor associated with over a twofold increased risk of PHLF (RR=2.3, 95 % CI=1.4–3.7, $p=0.001$).[26]

Similar to diabetes, obesity—another factor related to metabolic syndrome—has been associated with an increased risk of PHLF.[25] Schlindl et al. in a study of 104 patients who underwent major liver resection reported that the body mass

index (BMI) was higher among patients who experienced postoperative PHLF (median=29.9, SD=6.1) versus patient who did not (median=24.6, SD=4.2, $p<0.001$).[27]

Interestingly, malnutrition has also been associated with PHLF. The reasons for this are unclear, but may be due to an altered immune response in malnourished patients, as well as a decrease in hepatocyte regenerative capacity.[28,29] In a prospective study of 124 patients undergoing hepatectomy in Hong Kong, Fan et al. demonstrated that patients who were given perioperative nutritional therapy had a reduction in overall postoperative morbidity (34 vs. 55 %; RR=0.66; 95% CI=0.34 to 0.96), as well as less deterioration of liver function measured by rate of clearance of indocyanine green (−2.8 vs. −4.8 % at 20 min, $p=0.05$).[28]

Liver-Related Factors

Patients undergoing hepatectomy present with a wide range of underlying hepatic parenchymal disease including cirrhosis, steatosis, steatohepatitis, and chemotherapy induced liver injury that can affect the ability of the liver to regenerate after liver resection.

Cirrhosis is one of the most important and well-studied factors limiting the regenerative ability of the liver. Animal models have demonstrated that after resection, cirrhosis is associated with decreased levels of hepatocyte growth factor,[30] impaired transcription factors,[31] and a reduction of DNA synthesis, leading to lower volumes of regenerated liver.[32] Largely due to the risk of PHLF, mortality following liver resection has traditionally been associated with a high mortality, reaching 30 % in some series.[33,34] While mortality among cirrhotic patients has decreased over the past several decades, 90-day mortality following liver resection still remains higher than among patients without underlying cirrhosis. Not surprisingly, mortality is also associated with the degree of cirrhosis, as Capussotti et al. demonstrated that Child-Pugh class A patients had a lower in-hospital mortality versus Child-Pugh class B or C patients (4.7 vs 21.3 %, respectively; $p<0.001$).[35]

In addition to cirrhosis, steatosis and steatohepatitis can affect liver function and regeneration post resection. For example, an increased integrated stress response impairs regeneration of the liver in animal models in the setting of hepatic steatosis.[36] de Meijer et al. published a meta-analysis in which hepatic steatosis was noted to be a risk factor for increased perioperative morbidity and mortality in patients undergoing major hepatic resection.[37] Specifically, patients with at least 30 % steatosis had an increased risk both of postoperative death (RR=2.79, 95 % CI=1.19–6.51) and of developing postoperative complications (RR=2.01, 95 % CI=1.66–2.44) versus patients without steatosis.[37] In a recent different study that compared 174 patients with steatohepatitis or >33 % simple steatosis versus patients with a normal liver, 90-day postoperative overall morbidity (56.9 vs. 37.3 %; $p=0.008$), any hepatic-related morbidity (28.4 vs. 15.7 %; $p=0.043$), surgical hepatic complications (19.6 vs. 8.8 %; $p=0.046$), and hepatic decompensation (16.7 vs. 6.9 %; $p=0.049$) were all greater among patients with steatohepatitis versus those with normal liver parenchyma.[38]

With the increasing utilization of neoadjuvant chemotherapy, possible chemotherapy-related hepatotoxicity presents another factor that may impact the regenerative ability of the liver. Several studies have suggested that chemotherapy-associated liver injury is regimen specific. In a study of 248 patients who underwent neoadjuvant chemotherapy for colorectal liver metastasis (CRLM) followed by hepatic resection, Vauthey et al. reported that an oxaliplatin-based regimen was associated with sinusoidal dilation on pathologic analysis compared with chemotherapy-naïve livers (18.9 vs. 1.9 %, respectively; $p<0.001$; OR=8.3, 95 % CI=2.9–23.6).[39] In addition, irinotecan-based therapy was associated with steatohepatitis versus no chemotherapy (20.2 vs. 4.4 %, respectively; $p<0.001$; OR=5.4, 95 % CI=2.2–13.5) (Fig. 1). Of note, patients with steatohepatitis on pathologic review had an increased 90-day mortality compared with patients without steatohepatitis (14.7 vs. 1.6 %, respectively; $p=0.001$; OR=10.5; 95 % CI=2.0–36.4).[39] Robinson et al. corroborated these findings in a meta-analysis of 28 studies as neoadjuvant chemotherapy was associated with an increased risk of regimen-specific hepatic parenchymal injury.[40] Patients receiving oxaliplatin-based regimens had over a fourfold increased risk of sinusoidal injury compared with chemotherapy-naïve patients (95 % CI=1.36–13.97; $p=0.01$).[40] Several studies have associated sinusoidal injury and steatohepatitis with compromised liver regeneration as well as increased morbidity following hepatic resection.[41–44]

Surgery-Related Factors

In addition to patient- and liver-specific factors, the surgical procedure itself may influence the risk of PHLF in both the immediate postoperative period and in a delayed manner. Intraoperative blood loss and requirement of blood transfusion have been associated with an increase in postoperative complications following hepatectomy.[45,46] In a study of 1056 hepatectomies, intraoperative blood loss >1000 mL was strongly associated with the occurrence of major complications (OR=4.17; 95 % CI=1.04–17.5).[47] Excessive blood loss can lead to fluid shifts, which may induce bacterial translocation leading to systemic inflammation and coagulopathy, which predisposes for intra-abdominal hematoma and infection.[48,49] Moreover, postoperative blood transfusions required due to

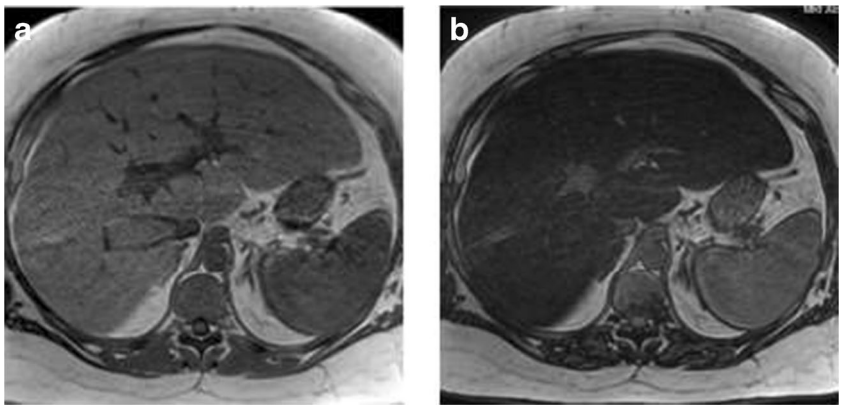

Fig. 1 MRI images of normal liver parenchyma and severe steatohepatitis. **a** In phase axial image of the liver showing normal liver signal. **b** Opposed phase axial image of the liver showing significant signal drop, indicating severe steatohepatitis in a patient following neoadjuvant chemotherapy

intraoperative blood loss, results an immunosuppressive effect that may contribute to PHLF.[50]

An important surgery-related factor is the extent of resection and avoidance of "small-for-size" liver remnant following hepatectomy. Much of the data regarding "small-for-size" liver remnant and resultant PHLF stems from the living donor liver transplant literature. First documented in 1996 by Emond et al., small for size graft syndrome initially was defined as graft-to-recipient weight ratio (GRWR) of less than 0.8 to 1.0 % or less than 30 to 50 % of standard/estimated liver volumes; small-for-size livers are associated with an increase in severe graft dysfunction with increased hepatocyte injury, hyperbilirubinemia, prolonged PT, portal hypertension, and ascites.[51–53] A similar "small for size" syndrome can be seen following extended hepatic resections, and therefore, one should take efforts to preoperatively predict adequate FRL in an effort to decrease the risk of PHLF.

While most surgery-related factors may result in an increased risk of PHLF in the immediate postoperative period, PHLF can also occur in a delayed fashion. Specifically, PHLF may be due to a combination of initial patient, liver, and surgery-related factors combined with a postoperative "second hit" such as infection or sepsis, which has been shown to decrease Kuppfer cell function and increase toxic cytokines both of which can inhibit hepatocyte proliferation in animal models.[54,55]

Physiology and Molecular Mechanisms of PHLF

Following hepatecomy, sheer stress on the vascular endothelium can be elevated due to an increase in portal pressure.[56,57] In turn, liver sinusoidal endothelial cells release nitric oxide in response to this increase in sheer stress with resulting sensitization of hepatocytes to hepatocyte growth factor (HGF).[58] HGF stimulates hepatocyte proliferation through activation of multiple signaling pathways as well as an increase in transforming growth factor alpha (TGF α). In addition, several portal hepatotrophic factors, including lipopolysaccharide, are initiated to assist in regeneration.[59] These portal hepatotrophic factors stimulate release of interleukin-6 (IL-6) from Kupffer cells that induces transcription of several cell division and survival genes.[60] In animal models of 70 % partial hepatectomy, 95 % of normally quiescent hepatocytes reenter the cell cycle and undergo mitosis peaking 24 h post-hepatectomy.[61] The resulting hepatocyte proliferation forms clusters of 10–14 unorganized "hepatic islands" that are not functional until connections are reestablished among hepatocytes and endothelial cells via extracellular matrix production by stellate cells.[62] While in animal models, restoration of liver volume occurs quickly (by 72 h post-hepatectomy), the original studies of healthy human hepatic regeneration showed volume restoration at 2 to 6 months with biologic function restored significantly earlier—in less than 3 weeks post major hepatectomy.[63] To facilitate normal hepatic metabolism and regeneration, constant interaction between hepatocytes and biliary endothelial cells is necessary. In the setting of PHLF, there is Kupffer cell dysregulation and a decrease in secretion of prostaglandin E2. This leads to hypersecretion of tumor necrosis factor resulting in necrosis, microvesicular steatosis, and irreversible hepatocyte injury that ultimately decreases the available exchange surface necessary for normal hepatic metabolism to occur.[64]

Preoperative Evaluation of Liver Function

Given the irreversible cellular injury and high mortality associated with PHLF, there has been great effort to preoperatively identify patients at high risk for hepatic dysfunction or failure. The preoperative assessment of a patient's risk of developing PHLF is performed using multiple different techniques to evaluate the quality and the quantity of the future liver remnant (FLR).

Quality Assessment of the Liver

Traditional Liver Function Markers and Clinical Scoring Systems

The correlation between PHLF and conventional laboratory parameters representing different synthetic and excretory functions of the liver such as alanine aminotransferase (ALT), aspartate aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin, lactate dehydrogenase (LDH), albumin and prothrombin time (PT) has been extensively reported in the literature.[65–72] None of these laboratory factors taken alone have been shown to provide an adequate evaluation of liver function; however, a combination of biochemical parameters has been included in different scoring systems to evaluate preoperative hepatic function.

In clinical practice, one widely used tool for assessment of liver function is the Child-Pugh classification that is based on five biochemical (bilirubin, albumin, and international normalized ration (INR)) and clinical (ascites and hepatic encephalopathy) variables.[73] The other clinical tool is the Model for End-Stage Liver Disease (MELD), which incorporates only three biochemical parameters (creatinine, bilirubin, and INR).[74] Both scoring systems were originally developed to grade chronic liver disease and cirrhosis in liver transplant candidates; however, both are currently also used to screen patients preoperatively for the risk of PHLF as well as to evaluate the perioperative liver function.[73,75,76]

Patients at the extreme of the Child-Pugh classification, such as those classified as advanced B or C (i.e., bilirubin> 50 μmol/L, serum albumin<2.8 g/dL, PT INR>2.3, moderate to severe ascites, and absence of hepatic encephalopathy), are not candidates for hepatectomy due to their risk of PHLF.[4] The use of the Child-Pugh classification to risk stratify patients with more modest or mild cirrhosis has demonstrated a relatively poor ability to predict specific PHLF-related mortality.[77] The role of MELD model as a preoperative predictor of PHLF has similarly been extensively evaluated with mixed results.[74,77–79] Several studies have suggested that MELD can be used in the preoperative setting to risk-stratify patients with regard to postoperative PHLF and death. In one study of 2056 patients, the laboratory values that comprise the MELD score were used to create a risk model in which a biological MELD higher than 10 was associated with a higher risk of PHLF and death.[80] A separate study from the Mayo Clinic reported on 772 patients with cirrhosis who underwent major surgery and noted that MELD was an independent predictor of 30- and 90-day postoperative mortality.[81] While Rahbari et al. noted that MELD score was correlated with morbidity and mortality following hepatectomy, the sensitivity for morbidity and mortality was only 55 and 71 %, respectively.[79] Cucchetti et al. reported that increasing MELD scores between postoperative days (POD) 3 and 5 was correlated with impending PHLF and should be a strong indication for intensive treatment.[78]

Indocyanine Green Retention Rate at 15 min

Preoperative evaluation for the risk of PHLF has included the use of the indocyanine green retention rate at 15 min (ICG-R15) test in some centers.[82,83] ICG is a water-soluble, nontoxic fluorescent dye that is injected intravenously and is eliminated almost exclusively by the liver. The absorption and emission spectrum of ICG are both in the near infrared range allowing for measurements to be performed by non-invasive monitoring.[10,65,84–90] The ICGR-R15 test has been shown to predict more accurately PHLF compared with both the Child-Pugh classification[91] and MELD model.[92]

There is no clear consensus on the cut-off value for ICG-R15 allowing for safe hepatic surgery. Fan et al. reported on 101 patients with cirrhosis who underwent major hepatic resection and suggested an ICG-R15 value of 14 % was the cut-off point that could maximally separate patients with and without high postoperative mortality (p=0.01).[93] In a separate study, Lam et al. reported that the cut-off value for a safe major hepatectomy could be increased to 17 % in relatively younger patients with an adequate remnant liver volume (RLV).[94] While the ICG-R15 test is used in the east, its adoption has not been widespread in western centers.

Other Liver Function Tests for the Quality Assessment of the Liver

Several quantitative estimations of liver function based on the principle of clearance of substrate by the liver have been developed. These substances include lidocaine,[73] galactose,[95] aminopyrine,[96], amino acid,[97], and methacetin.[98] None of these various tests have been proven to be superior than ICG-R15 for the prediction of PHLF- or PHLF-related mortality.[91] There are also several tests available that are based on the synthetic functions of the liver including serum levels of hyaluronate[99] and type IV collagen,[100] energy production of the liver (arterial ketone body ratio),[101] and the number of receptors for asialoglycoprotein (technetium-99 m-galactosyl-human serum albumin; 99 m Tc-GSA scan).[68,102–106] While these tests may provide important information regarding the quality of the remaining liver remnant, their high cost and complexity are barriers to their clinical implementation.[91]

Liver-Specific Agents for Contrast-Enhanced MRI

There is an increasing interest in the possibility of integrating both quantitative and qualitative assessments of the functional liver remnant. In particular, the role of magnetic resonance imaging (MRI) for assessment of the liver is well established.

Recently, liver-specific contrast agents have been developed which both improve morphological assessment as well as provide functional information.[107] The most promising liver-specific contrast agent for predicting PHLF after major liver resection is gadoxatic acid.[108] After intravenous injection, this gadolinium-based paramagnetic contrast agent is taken up by functional hepatocytes and excreted into bile ducts via membrane transporters. The temporary accumulation of this contrast agent in the liver and subsequent enhancement of the normal liver parenchyma permits the measurement of relative liver enhancement (RLE).[109] Wibmer et al. reported that the preoperative RLE was strongly related to the probability of developing PHLF compared with both the "50-50 criteria" (OR=0.935, 95% CI=0.884–0.990; p=0.020) and the International Study Group of Liver Surgery (ISGLS) grading system (OR=0.967, 95 % CI=0.951–0.982; p<0.001).[62]

Quantity Assessment of the Liver

Future Remnant Liver Volume

Preoperative determination of the FLR size after hepatectomy is fundamental for effective and safe hepatic resection. Currently, there is no uniform consensus regarding the limit of the FRL volume necessary to achieve a "safe" liver resection or the modality most effective for evaluating FLR size preoperatively.[110] Several studies have tried to validate different imaging techniques for liver volumetry including conventional ultrasound[111] and three-dimensional ultrasound[112]; however, the techniques most frequently utilized to assess FLR include computed tomography (CT) and MRI.[113] Both imaging techniques permit the calculation of the FRL volume, as well as the ratio of FRL volume to the total functioning liver volume (TLV) (Table 2).[39,44,110,114–118]

In a consensus conference on the surgical management of liver metastasis, an expert panel conclude the "acceptable" FLR to be >20 % of TLV for patients with a normal liver, >30 % of TLV in patients with evidence of steatosis/steatohepatitis, and >40 % of TLV in patients with hepatic fibrosis or cirrhosis.[119] Ribero et al. confirmed validated these cut-offs in a study of 112 patients with differing status of underlying liver disease (normal, steatosis, fibrosis, or cirrhosis) who underwent major hepatectomy.[120] Specifically, in the group of patients with a FLR<20 % of TLV, the rate of post-operative liver-related complications and hepatic insufficiency was 90 and 30 % compared with 23 and 2 %, respectively, in the group of patients with a FLR>20 % of TLV (p<0.001 and 0.009). Moreover, in a recent study of 301 patients who underwent extended right hepatectomy, Kishi et al. reported that a FLR<20 % of TLV was the strongest predictor of PHLF (OR=3.18; CI 95 %=1.34–7.54) on multivariate analysis.[121]

Criteria for Defining and Predicting the Post Hepatectomy Liver Failure

Prior to this decade, there has been no uniform definition of PHLF. In 2011, the International Study Group of Liver Surgery (ISGLS) reviewed more than 50 studies on hepatic resection between 2003 and 2009, using multiple criteria to define PHLF.[5] In turn, the definition of PHLF involves acquired deterioration of one or more synthetic, excretory, or detoxifying functions of the liver including hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT) or international normalized ration (INR), elevated serum lactate, and hepatic encephalopathy during the post-operative period.[5]

In clinical practice, the most commonly used criteria for defining, predicting, and grading the severity of PHLF are the "50–50 criteria,"[18], peak bilirubin >7 mg/dL,[19], the ISGLS criteria,[5] and the more recent risk score proposed by Hyder et al. (Table 3).[80]

50–50 Criteria

In an effort to refine the definition of PHLF and its grades of severity, Balzan et al. proposed the "50-50 criteria".[18] The criteria for PHLF consisted of a combination of PT <50 % (INR>1.7) and serum bilirubin level >50 μmol/L (>2.9 mg/

Table 2 Formulas to determine FLR

Reference	Year	Formula	Threshold for hepatectomy
Yamanaka et al.[114]	1994	−84.6+0.933×PHRR+1.11×ICG-R15+0.999×age	45
Kubota et al.[44]	1997	(resected volume-tumor volume)/(TLV-tumor volume)	40 % non-tumorous parenchyma
Vauthey et al.[118]	2000	(CT FLR)/(706×BSA+2.4)	20 % in normal livers
Ribero et al.[117]	2008	(CT FLR)/(−794+1267×BSA)	20 % in normal livers
Uchiyama et al.[115]	2008	164.8−0.58×albumin−1.07×hepaplastin test+0.062×glutamate oxaloacetate transaminase−685×ICG-K−3.57×oral glucose tolerance test linearity index+0.074×weight of resected liver	25
Du et al.[116]	2011	ICG-K x 22.487+standardized remnant liver volume×0.02	13.1

Table 3 Predictive models of PHLF

Preoperative Models	Description	Validation studies
MELD Score	A scoring system used for determining the gravity of end-staged liver disease. Takes into account serum creatinine, bilirubin, INR, and dialysis status	74,77
Child-Pugh Score	Child-Pugh scoring system is used for grading liver cirrhosis into three distinct classes. Takes into account serum bilirubin, albumin, INR, ascites, and encephalopathy.	77
Nanashima et al.[149]	GSA, serum bilirubin, hyaluronate, and major hepatectomy were used to construct a regression formula. A cut-off for high risk was introduced.	-
Postoperative Models	**Description**	**Validation studies**
MELD Score	A scoring system used for determining the gravity of end-staged liver disease. Takes into account serum creatinine, bilirubin, INR, and dialysis status.	78,79
Child-Pugh Score	Child-Pugh scoring system is developed for grading liver cirrhosis into three distinct classes. Takes into account serum bilirubin, albumin, INR, ascites, and encephalopathy.	-
50-50 Criteria[18]	The 50–50 criteria state that a combined prothrombin time less than 50 % and a serum bilirubin of more than 50 μmol/L on POD 5 is a significant predictor of postoperative mortality due to PLF.	79,80,122,123,150
Kim et al.[150]	Kim et al. proposed the 50–50 criteria to be adjusted to the combination of PT <65 % and bilirubin ≥38 μmol/L on POD 5.	
Snap peak bilirubin >7 mg/dL[19]	A postoperative peak bilirubin greater than 7 mg/dL was found to be a significant predictor of death as a result of liver failure.	80,122
ISGLS Definition[5]	The ISGLS proposed the general definition of a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR and hyperbilirubinemia on or after postoperative day 5. To be divided further into grade A, B, or C.	79,122
Hyder et al.[80]	A composite integer-based risk score based on international normalized ratio, bilirubin, creatinine, and complication grade at POD 3.	-

dL) recorded on POD 5.[18] In this study, patients who met these criteria had a 59 % risk of early postoperative mortality versus only a 1.2 % risk of mortality in patients for whom both these conditions were not fulfilled ($p<0.001$). In the original study, the accuracy of the "50-50" criteria to predict in-hospital mortality was 97.7 % (95 % CI=96.6–98.7 %; sensitivity=69.6 %; specificity=98.5 %).[18]

The role of the "50-50 criteria" as a predictor of postoperative mortality due to PHLF is still, however, unclear. While several studies have confirmed the ability of the "50-50" criteria to predict post-hepatectomy PHLF-related mortality,[79,122,123] other studies have noted a much more modest performance of the "50-50" criteria.[19,80] For example, in one large series of 1286 patients undergoing hepatic resection, only 14 of 28 patients who died fulfilled the "50-50 criteria".[19] In a second study of 2056 patients who underwent liver resection, on postoperative day 5, only 60 (4.7 %) patients had a bilirubin ≥2.9 mg/dL, 3 (0.2 %) patients had an INR ≥1.7, and only 1 (0.07 %) patient had the requisite combination of both bilirubin ≥2.9 mg/dL and INR≥1.7.[80]

Peak Bilirubin >7 mg/dL

Mullen and colleagues have suggested that, rather then the "50-50" criteria, only peak bilirubin be utilized to define PHLF.[19] In a large retrospective study of 1059 patients who underwent major hepatectomy at three high volume centers in the USA and Italy from 1995 to 2005, a peak postoperative bilirubin greater than 7 mg/dL was the most powerful independent predictor of any complication (OR=83.3), major complication (OR=10.0), 90-day mortality (OR=10.8), and 90-day PHLF-related mortality (OR=250, all $p<0.001$).[19] The authors reported an area under the curve (AUC) of 0.982, with a sensitivity and specificity of 93.3 and 94.3 %, respectively (Fig. 2).[19]

While some studies have subsequently validated a peak bilirubin of 7 mg/dL,[121] others reports have questioned the overall accuracy and clinical applicability of this parameter as the sole means to predict post-hepatectomy PHLF-associated death.[80,124] In one study, of the 2056 patients who underwent either minor or major hepatectomy, only 20 patients demonstrated a peak bilirubin concentration >7 mg/dL.[80] Of the 20 patients, five (25 %) died within 90 days for a sensitivity and specificity of the >7 mg/dL rule of 25 and 99.3 %, respectively, with a poor overall accuracy (AUC=0.574).[80]

ISGLS Definition

More recently, in 2011, the ISGLS defined PHLF as an increase in INR and concomitant hyperbilirubinemia on or after POD 5.[5] Grades of PHLF severity were also defined depending on the patient's clinical management: mild disruption of liver function (normal trend after hepatectomy) not requiring management (Grade A); moderate liver dysfunction not requiring invasive therapy (Grade B); and severe dysfunction, requiring invasive therapy (Grade C) (Table 4).[5]

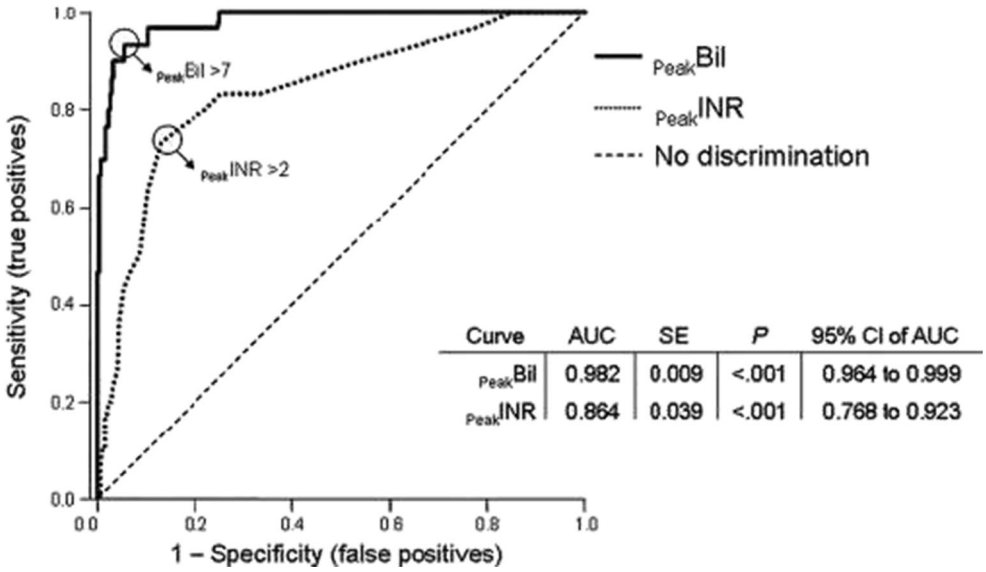

Fig. 2 Receiver operating characteristic (ROC) curves demonstrating that the cut-off peak postoperative bilirubin ($_{Peak}$Bil) value to predict liver failure-related death is 7.0 mg/dL (area under the curve [AUC] 0.982; sensitivity 93.3 %; specificity 94.3 %). Reprinted with permission[19]

This clinical risk score was validated in a study of 807 patients who underwent hepatic resection that showed the ISGLS criteria for PHLF to be an independent predictor of mortality.[79] However, despite efforts by the ISGLS to define PHLF more accurately to predict prognosis early after hepatectomy, several studies have questioned the accuracy of the ISGLS criteria. Specifically, Skrzypczyk et al. compared the ISGLS definition with the "50-50 criteria" and peak bilirubin >7 md/dL criteria among 680 patients who underwent either minor or major hepatectomy.[122] In this study, the ISGLS definition was found to be the least predictive of both the occurrence of major complications (positive predictive value of 49.2 % for ISGLS vs. 78.9 % for "50–50 criteria" and 65 % for peak bilirubin >7 md/dL), as well as the risk of postoperative death (OR=6.9 for ISLGS vs. OR=21.1 for "50-50" and OR=21.7 for peak bilirubin >7 md/dL).[122]

Hyder et al. Risk Score

In light of prior shortcomings, Hyder et al. proposed the use of an integer-based risk score that combines Clavien-Dindo complication grade, INR, bilirubin, and creatinine level on POD 3.[80] In this study, the proposed model had the ability to estimate a numerical risk of developing PHLF, as well as to predict post-hepatectomy 90-day mortality with high accuracy.[80] Specifically, when patients were stratified according to the number of points derived from the aforementioned risk score, there was an incremental increased risk of death (<5.9 points, 0.2 % vs. 6.0 to 8.9 points, 1.2 % vs. 9.0 to 10.9 points, 34.3 % vs. ≥11 points, 83.3 %; $p<0.001$). Among patients who had ≥11 points, the prediction score had a sensitivity of 83.3 % and specificity of 98.9 % (Fig. 3).[80] Future studies will need to validate this integer-calculator-based risk score of PHLF and death proposed by Hyder et al.

Strategies to Prevent Post-Hepatectomy Liver Failure

Given the association of the FLR remnant volume and risk of post-hepatectomy liver function, increasing the remnant volume has been the rationale behind several preoperative

Table 4 Consensus definition and severity grading of posthepatectomy liver failure (PHLF) by the International Study Group of Liver Surgery (ISGLS) (Reprinted with permission)[5]

Definition	A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively<comma>PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out.
Grade	
A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient.
B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

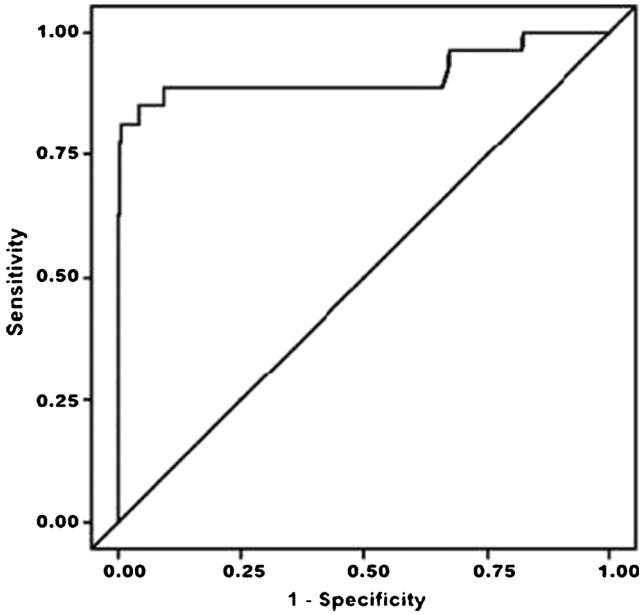

Fig. 3 Receiver-operating characteristic (ROC) of the Hyder et al. composite prediction rule. The composite score consists of weighted values for grade of postoperative complication, as well as INR, bilirubin, and creatinine on POD 5. ROC curve analysis resulted in an area under the curve [AUC] 0.927. Reprinted with permission[75]

procedures.[125,126] Portal vein embolization (PVE) was first described in the 1980s as a technique to increase the remnant liver volume by Kinoshita[127] and later by Makuuchi et al.[128] PVE is typically an ultrasound-guided percutaneous procedure that induces liver hypertrophy following embolization of the portal vein ipsilateral to the side of disease. The blockade of the portal vein results in hypertrophy of the contralateral side and thus an increase in the size of the FLR. PVE also results in an increase in the production of hepatic growth factor (HGF) and TGF, along with redistributing the portal blood flow to the FRL. PVE allows for hypertrophy of the FLR by 30–40 % within 4–6 weeks in more than 80 % of patients.[57] A meta-analysis of 1088 patients who underwent preoperative PVE for major liver resection demonstrated that 4 weeks after PVE, 85 % of patients were able to undergo the planned hepatectomy with an 8 to 27 % increase in FLR.[129]

In some circumstances, a surgeon may prefer portal vein ligation (PVL) rather than PVE. Specifically, PVL has been proposed in those cases in which resection of bilobar malignant liver lesions requires a two-stage approach due to inadequate FLR volume.[130,131] With this approach, clearance of the FLR is performed using a parenchymal sparing resection approach. At the time of the first surgery, the contralateral portal vein is ligated. Three to six weeks following the first stage after allowing time for hypertrophy of the FLR, the second stage is performed which consists usually of an extended/major hepatectomy. A meta-analysis reported that there was no statistically significant difference comparing PVE and PVL in terms of increasing FLR volume (+39 % after PVE vs. + 27 % after PVL; p=0.06), morbidity (RR=1.08, 95 % CI= 0.55–2.09; p=0.83), and perioperative mortality (RR=0.87, 95 % CI=0.19–3.92; p=0.85).[132]

In 2011, a third strategy combining in situ liver partition, PVL followed by hepatectomy (ALPPS) in a two-stage surgical approach was developed to decrease the time between PVL and resection for patients with borderline FRL volume.[133] This approach allows for clearance of one side of the liver while maintaining the main liver mass in place to assist with liver function while the FLR hypertrophies in order to avoid PHLF. ALPPS may also facilitate superior hypertrophy of the FLR compared with PVE, with a reported 74 % volume increase of the remnant liver in a mean of 9 days.[133] Schadde et al. reported on 202 patients who underwent ALPS S and noted that a median starting standardized FLR of 21 % increased by 80 % within a median of 7 days, in contrast to approximately 8–27 % within 2–60 days by PVL/PVE.[134] In a recent meta-analysis, reviewing the increase in FLR after different procedures, Pandanaboyana et al. reported that ALPPS provided an additional 17 % increment of the FLR compared with PVE (p=0.03).[132] Although these results are promising, the ALPPS procedure has been reported to have high operative morbidity (16–64 % of patients) and perioperative mortality (12–23 % of patients), which has prevented it from becoming widely utilized.[134]

Treatment of Post-Hepatectomy Liver Failure

While patients are ideally screened preoperatively and any comorbid conditions optimized in an attempt to avoid PHLF, patients should also be monitored closely postoperatively with treatment initiated at any early indication of PHLF. Particular attention should be paid to early clinical and laboratory signs of liver failure including changes in coagulation factors (including PT and INR), bilirubin, as well as signs of encephalopathy. Patients should also be monitored for early signs of infection, hemodynamic failure, renal failure, malnutrition, or metabolic disorders so that these may be addressed at an early stage.[135,136] Patients who develop any of these complications should be monitored in an ICU setting, and the use of hepatotoxic as well as nephrotoxic medications should be avoided.

Generally, the management principles for PHLF resemble those suggested by the American Association for the Study of Liver Diseases (AASLD) for the management of acute liver failure (ALF).[137] The severity of the PHLF should be followed using laboratory values such as INR, platelets, ammonia, bilirubin, and creatinine. Resuscitative measures and organ support provide the optimal environment for liver regeneration. In early stages of encephalopathy, ammonia levels should be followed and lactulose, polyethylene glycol, or

rifaximin used for treatment.[138,139] Volume depletion should be monitored and addressed by fluid replacement. Fluid-refractory hypotension may warrant the use of vasopressor agents. Acute renal failure is common in ALF and associated with increased mortality. Causes may be multifactorial, including direct drug toxicity, acute tubular necrosis, or the presence of the systemic inflammatory response syndrome.[140] The administration of antibiotics in patients suffering from ALF is associated with a significant decrease in infectious complications and therefore early use of antibiotics may also be advantageous in patients suffering from PHLF.[141] Hypoglycemia is seen in up to 45 % of patients with acute liver failure, and thus, glucose levels must be monitored and dextrose infusion used as necessary.[142] There is still no widely effective treatment of PHLF once it has befallen the patient. Albumin, fresh frozen plasma, and antithrombin III may be used to support clotting factors depleted during liver failure.[143]

The introduction of the molecular absorbent recirculating system (MARS®), an extracorporeal albumin dialysis machine, was shown to be effective in bridging patients with fulminant liver failure to orthotopic liver transplant (OLT).[144] Its use in PHLF, however, has been sparsely studied; while improvement in biochemical parameters has been reported with use of MARS for PHLF, there has been no demonstrable survival benefit.[137,145,146]

While rescue OLT remains the most definitive treatment for PHLF, such treatment is not universally available for many patients who develop PHLF. In fact, less than 10 % of liver transplantations are performed in patients with ALF and OLT for PHLF has only been sparsely reported.[147,148] Given that the initial indication for hepatic resection frequently involves a malignancy outside of transplantation criteria, salvage OLT for PHLF is often not feasible.

Conclusion

PHLF is a major cause of postoperative morbidity and mortality in patients following major hepatectomy. Physiologically, with the onset of PHLF, there is induction of irreversible structural damage and hepatocyte injury in the regenerating liver. Adequate preoperative risk assessment and maximal increase of FLR using PVE, PVL, or ALPPS are essential for PHLF prevention. Early diagnosis and treatment of postoperative complications following hepatic resection are essential to mitigate the risk of PHLF. Once PHLF occurs, treatment largely revolves around supporting organ function, use of colloid and crystalloid products, as well as maximal treatment of associated complications. Short of OLT, no definitive "curative" treatment of PHLF exists. Future studies should be aimed at understanding the mechanisms and risk factors of PHLF, as well as targeting means to better avoid and treat this challenging post-hepatectomy complication.

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