Revised version – R.1.

Post hepatectomy liver failure (PHLF) – Recent advances in prevention and clinical management

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Text : **5027**
Abstract : **248** words
References : **102**

Abstract

Background: Posthepatectomy liver failure (PHLF) is a relatively rare but feared complication following liver surgery, and associated with high morbidity, mortality and cost implications. Significant advances have been made in detailed preoperative assessment, particularly of the liver function in an attempt to predict and mitigate this complication.

Methods: A detailed search of PubMed and Medline was performed using keywords "liver failure", "liver insufficiency", "liver resection", "postoperative", and "post-hepatectomy". Only full texts published in English were considered. Particular emphasis was placed on literature published after 2015. A formal systematic review was not found feasible hence a pragmatic review was performed.

Results: The reported incidence of PHLF varies widely in reported literature due to a historical absence of a universal definition. Incorporation of the now accepted definition and grading of PHLF would suggest the incidence to be between 8-12%. Major risk factors include background liver disease, extent of resection and intraoperative course. The vast majority of mortality associated with PHLF is related to sepsis, organ failure and cerebral events. Despite multiple attempts, there has been little progress in the definitive and specific management of liver failure. This review article discusses recent advances made in detailed preoperative evaluation of liver function and evidence-based targeted approach to managing PHLF.

Conclusion: PHLF remains a major cause of mortality following liver resection. In absence of a specific remedy, the best approach is mitigating the risk of it happening by detailed assessment of liver function, patient selection and general care of a critically ill patient.

Introduction

Liver resection has become a safe and a well-accepted treatment for a variety of primary and secondary tumors with excellent outcomes and acceptable morbidity [1]. Mortality after a liver resection varies from about 2% for colorectal metastases to about 10% for biliary tumors and hepatocellular carcinomas although some older series have even reported much higher rates, up to 30% for major liver resections involving over 4 segments [2, 3]. Non-lethal complications after liver resections are frequently encountered in up to 45%, and vary from less severe incidents to life-threatening complications, including infections or sepsis, bleeding, leakage, or cardiopulmonary events [4, 5]. Post-hepatectomy liver failure (PHLF) is a feared and severe complication after liver resection and its incidence is higher after resection for hepatocellular carcinoma(HCC) and hilar cholangiocarcinoma compared to liver resection for colo-rectal liver metastases(CRLM) [6, 7], resulting in increased morbidity and mortality[3, 8-11]. In a large study, PHLF criteria were satisfied in 70% of patients who died following a liver resection for all indications, with PHLF being the direct cause of death in over half of those [11]. Moreover, nearly half of in-hospital mortality due to PHLF occurs within 30 postoperative days [12]. Furthermore, significant costs are associated with management of these complications, and more so when the attempts to salvage from complications fail [5, 13].

Although many treatment strategies have been entertained to rescue the patient with PHLF, the evidence for these managements is still limited, with only few of these routinely employed in a clinical setting[8 , 9, 14].

The aim of this narrative review, based on a selection of relevant and recent literature, is to discuss recent advances in work-up and risk assessment of patients undergoing major liver resections and to explore the best current evidence in management of PHLF.

Literature search

An electronic literature search in the databases of PubMed and Medline using keywords relating to "liver failure", "liver insufficiency", "liver resection", "postoperative", and "post-hepatectomy" was done. Detailed search of published literature particularly over the last 5-10 years revealed that whilst there were many articles written about PHLF, none of these was a systematic review as such. The literature concentrated variously on etiology and pathogenesis of PHLF whilst many others discussed preoperative and intraoperative strategies to minimise the occurrence of PHLF. Almost all discussed in varying degrees of details, the basis of management of PHLF. At the outset, the aim of our manuscript was to focus on the modern investigations employed towards work-up of patients with liver disease and investigate new evidence-based protocols for preoperative risk-assessment of patients undergoing liver resections for various indications. Hence, specific emphasis was placed on such literature Therefore, a formal systematic review was not found feasible based on the heterogeneous patterns of the identified articles, and a pragmatic approach was chosen, with more attention paid to pertinent literature published after 2015. Only published full-text papers written in the English language were considered.

Definition of PHLF

Hepatic insufficiency occurring after partial resection of the liver, or more precisely described as *post hepatectomy liver failure* (PHLF), has been described by the use of a variety of definitions in the literature[15-17] (**Table 1**). Several definitions have not reached clinical use because the risk calculations were based on complicated formulae or more or less obscure laboratory tests(e.g., hapaplastin test by Eguchi et al[18]). The "50–50 criteria" (PT<50% and

bilirubin > 50µmol/l on POD 5) were introduced by Balzan and coworkers[15] in 2005 and validated in 2009 as a useful predictor of death after liver resection [19]. A grading score of liver failure severity based on available blood tests and clinical observation was suggested in 2005 by Schindl et al[16]. Currently, the International Study Group of Liver Surgery (ISGLS) definition[3] of 2011 has now been widely embraced as a standard to describe the PHLF. This entity involves the acquired deterioration of one or more synthetic, excretory, or detoxifying functions of the liver, including hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT) or an international normalized ratio (INR), elevated serum lactate, and hepatic encephalopathy during the postoperative period (**Table 2**).

Epidemiology

The reported incidences of PHLF have varied tremendously, between 0.7 and 34%[3, 20], although a PHLF incidence of between 8–12% is more commonly described in recent reports [12, 21, 22]. This wide range in incidences may partly be explained by the use of different definitions of PHLF, but likely also by variations in the extent of liver surgery and the case-mix of the patients included in the studies reported.

Work-up for a patient undergoing a major liver resection.

The aim of a detailed work-up for any patient undergoing major liver surgery, particularly for HCC, is manifold. Apart from accurately staging the disease and estimating prognosis, it involves evaluation of the patient's general health, analysis of liver function, identification and modification, if possible, of pre-operative risk factors and mitigating the effects of postoperative complications, particularly PHLF.

A number of preoperative factors can potentially contribute towards PHLF[6, 8, 23, 24]. These have been extensively investigated and discussed in other manuscripts and are listed in **Table 3**. These include patient factors, disease pathology, intraoperative features and postoperative course. Whilst many of these can be mitigated, probably the single most important factor that influences the occurrence or otherwise of PHLF is the status of the liver. Hence it is quite important to evaluate liver function in as much detail as possible. The rest of the discussion in this section, therefore, concentrates on recent advances in preoperative assessment of liver function

Biochemical evaluation of liver function

For decades the Child-Pugh(C-P) score has served as an essential tool for prognostication in patients with chronic liver disease and is to some extent still a guiding factor in clinical decision-making[25] [26]. The MELD score ('Model for End-stage Liver Disease') eventually turned out to be a better predictor of prognosis in chronic liver disease. More importantly, the MELD score was relevant in the early prediction of morbidity and mortality after liver resection[27].

Although the Childs-Pugh score is still routinely used in many liver surgery protocols, it was somewhat subjective and not necessarily evidence-based. More recently, the Albumin-Bilirubin (ALBI) score and its modifications have been proposed as an objective and evidence-based method of assessment of the clinical liver function [28]. This has been validated as a reliable assessment of liver dysfunction in the original and subsequent studies, both in Eastern and Western populations[29, 30] and has also been found to be superior to the Childs-Pugh score in predicting outcomes after liver resection for HCC[31]. Incidentally, ALBI score and its modifications have also been found to correlate with ICG-clearance algorithms with a somewhat better predictive value[28].

As mentioned earlier, Child-Pugh score was never meant to prospectively prognosticate outcomes after liver resection for HCC but nevertheless, it has been used to stratify preoperative risk. The ALBI score and it's modifications, however, have been examined not just to grade liver disease but also to specifically investigate prognosis of HCC after curative management, both resection and transplantation. In two large retrospective studies[30, 31], ALBI grade predicted both short and long-term mortality after potentially curative treatment of HCC. Moreover, it provided better correlation than traditional tests such as Childs-Pugh score and ICG clearance. However, to our knowledge, this has not been specifically employed in a preoperative algorithm to select patients suitable for undergoing liver resection for HCC.

Volumetric assessment of liver function

Assessment of the future liver remnant volume (%FLR) by computer tomography(CT) according to defined protocols is achieved by calculating the proportion of remaining liver tissue of the total liver volume and is explained in more detail elsewhere[32]. To possibly avoid PHLF, the %FLR was empirically suggested to be at least 20% of the standardized total liver volume, given that the remaining parenchyma is normal[32, 33]. Moreover, Truant et al. found that the remnant liver volume(RLV=%FLR) related to the bodyweight provides added relevant information and showed that patients with anticipated RLV <0.5% of their body weight were at considerable risk for postoperative hepatic dysfunction and mortality[33]. If the liver is compromised, either by chemotherapy treatment or pre-existing liver disease(e.g. cirrhosis), an increased %FLR of at least 30% and 40% respectively, is required [26, 34]. However, it is amply clear that liver volume, although important per se, does not necessarily

correlate with liver function which in turn are related to various factors such as liver pathology, steatosis, chemotherapy and parenchymal function, in general [28, 35, 36].

Traditional factors that have been proposed as relative contraindications for liver resection are small future liver remnant/FLR) volumes, Child-Pugh scores B and C, hepatic portal pressure gradient(HVPG) of less than 10 mmHg, elevated serum bilirubin, platelet count < 100 000 and indocyanine green retention test after 15 minutes(ICG R15) < 15–20% [26, 37, 38]. However, many of these are not absolute. There are inherent limitations with liver volumetry and Child-Pugh scores whilst estimation of HVPG entails an invasive process, and cut-off values are considered to be too restrictive[39]. Meta-analyses have shown these values to be more predictive of PHLF in the Eastern than the Western population[40, 41]. However, in recent years, there have been many advances in the functional assessment of liver disease and liver volumes which are likely to supersede these traditional investigations.

Assessment of functional liver remnant and functional liver volume

Assessment of *functional* liver remnant volume is superior, compared to a simple calculation of future liver *volume* (%FLR) [42, 43]. Amongst the myriad of tests used to assess functional liver volume, the indocyanine green clearance (ICG R15) has been the most commonly used test, at least in Eastern centers, resulting in a useful algorithm devised to minimize PHLF and mortality following liver resection[44]. In a large single-centre study, the authors strictly applied an algorithm based on bilirubin and then stratified according to ICG clearance not only to decide what patients to subject to a resection but also what type of resection to perform. Excellent results were achieved over a 10-year period with exceptionally low mortality of only 1 patient in over a thousand resections[44].

Moreover, Maruyama et al[45] recently reported on the evaluation of the future *liver remnant function* after portal vein embolization(PVE) by use of the future liver remnant ICG clearance rate(ICGK-F), and they found that ICGK-F was more useful for predicting PHLF than %FLV [45]. However, some limitations of the ICG clearance, particularly in perioperatively jaundiced patients [46] and in those with hemodynamic compromise, are well known.

More recently, the Methacetin breath test, which evaluates whole liver function by detecting the $^{13}CO_2/\ ^{12}CO_2$ ratio in expired air, derived from the rate of metabolization of ^{13}C-methacetin by P450 1A2 (CYP1A2) in hepatocytes has been increasingly used, particularly in the Western population [47]. A further algorithm, similar to the one above for ICG clearance, has been proposed for clinical practice[48]. The Methacetin test algorithm was used in a large series of patients undergoing liver resections for all indications. The authors reported a significant reduction in incidence of PHLF (24.7% to 9%) and liver-related postoperative mortality (4% to 0.9%) with the application of the algorithm despite a corresponding increase in the numbers, both of complex resections and patients with established cirrhosis[11]. However, both these tests provide a global evaluation of the liver, assuming that liver function is uniform throughout the parenchyma. It is, however, far more valuable to assess regional liver function, particularly of the proposed FLR. Intraoperative ICG clearance test has been employed to assess "real-time" functional liver volume [49, 50]. More recently intraoperative use of the Methacetin breath test was also evaluated in pilot study, however, no definitive conclusion can be currently drawn[51].

Radiological assessment of fractional and regional liver function

Various specialist radiological investigations have been more effective in quantifying the FLV better. One of the earlier tests more recently adopted into clinical practice is an excretion test based on 99m Technetium mebrofenin (99m Tc-mebrofenin scintigraphy), which uses a

similar pharmacological pathway as ICG clearance. Although it has some limitations, better correlation is achieved in combination with conventional volumetry techniques. Complex equations are then better able to predict pre-operative regional liver function and PHLF[52, 53]. Another test that was developed to precisely map regional liver function, particularly in diseased livers is the 99mTc-GSA SPECT[54]. Since it utilizes a different metabolic pathway, it can potentially be used in patients with jaundice and obstructed biliary tree. In combination with spatial CT images, it provides an estimation of functional rather than a plain volumetry. Its best use, potentially, would be in surgery for hilar cholangiocarcinoma and in ALPSS surgery [55]. However, it has predominantly been used in the far-east, mostly due to the complexity and need for specialist equipment but has yet to be routinely utilized in the western population for further evaluation.

Finally, another image-based estimation of regional liver function, which shows promise, is the Gd-EOB-DTPA enhanced magnetic resonance imaging(EOB-MRI)[56]. It uses a standard MRI scanner without the need for any specialist equipment. The EOB-MRI is reported to improve the prediction of PHLF in patients suggested for liver resection, even in patients that have undergone PVE, with an accuracy of 80.8% [57]. Moreover, it was found to correlate well with the methacetin clearance, a functional excretion test[56]. However, it is still in its infancy, and the conditional settings and the best imaging protocols are yet to be determined.

Although some of these non-invasive radiological investigations do look promising, their use has yet to be translated into clinical algorithms either for ruling patients out of surgery or those specifically aimed at improving PHLF and perioperative mortality

PHLF – diagnosis and differential diagnosis

As discussed earlier, the diagnosis of PHLF is based on derangement of liver function, coagulopathy, high lactate, and emerging encephalopathy. Although the early diagnosis of PHLF is desirable, deranged liver function tests(LFTs) are in general commonly encountered in critically ill patients. These can be further confounded in patients with sepsis. In an observational study of patients without the hepatobiliary disease, abnormal liver enzymes were found in up to 61% of patients admitted to a critical care unit and were shown to correlate with in-hospital mortality[17]. However, in the majority of patients, the abnormalities were less than twice the normal upper values. Elevation of bilirubin over twice the upper limit of normal was also found to correlate with much higher mortality [58].

Cholestasis is not uncommon in critically ill patients. A variety of factors lead to cholestasis and elevated bilirubin in critically ill patients, including drugs, parenteral nutrition, bacterial translocation, and biliary sludge. At a cellular level, there is significant up or downregulation of bile salt transporters [59]. Hence, hyperbilirubinemia in critically ill patients need not always be related to cholestasis alone.

Hepatic hypoxia is frequently encountered in critically ill patients with organ failure. Intraoperative factors such as significant blood loss, prolonged episodes of hypotension, and long inflow occlusion times contribute to significant hepatic ischemia. Hepatic hypoxia is an independent risk factor for prolonged critical care stay and higher mortality [60]. Moreover, liver congestion and increased stiffness is common after major liver resection and is frequently seen in small for size syndrome. This can be further exaggerated postoperatively by fluid overload, mechanical ventilation, and cardiac dysfunction. Higher liver stiffness, even in non-cirrhotic patients, correlates with higher in-hospital and long-term mortality [61]. Liver stiffness measurement(LSM) has been accepted as a proxy for liver cirrhosis and has been evaluated by commercially available ultrasound types of equipment. Nishio et al found

that the LSM provided independent predictive information for the risk of PHLF, but also added reliable and clinically useful information as to the functional remnant liver after resection in patients with HCC[62].

Management of PHLF – general principles

Occurrence and resolution of PHLF is closely related to optimum liver regeneration[63, 64], and all therapeutic measures should essentially aim to satisfactorily promote it. However, specific evaluation of the extent and progress of postoperative liver regeneration is quite difficult. Although in theory, serial evaluation of growth factors markers and cytokines could predict the extent and success of liver regeneration, there is a lack of firm clinical evidence that they do[64].

In the absence of any randomized data specifically related to the management of PHLF, general principles of management of acute liver failure (ALF) and organ dysfunction apply. These have remained the same over the years and incorporate principles of management of ALF from any cause, goal-directed therapy for organ dysfunction, and identifying and treating reversible factors in the postoperative period[14, 65, 66].

Identification and management of remediable causes

Significantly higher bilirubin level is seen in PHLF as opposed to other generic causes and it not only helps diagnose PHLF but is also of prognostic relevance[67]. Obstructive causes of hyperbilirubinemia must be looked for and reversed by a radiological or operative intervention. Vascular inflow or outflow compromise of the liver remnant may rarely occur, particularly in the early postoperative period, and can lead to hepatic ischemia/ congestion. The risk of inflow thrombosis is higher if skeletonization of hepatoduodenal ligament or vascular reconstruction of inflow has been performed[68]. Venous outflow can also be compromised by torsion of the left liver remnant following a major right resection[69].

Similarly, skeletonization of hepatic veins can lead to outflow thrombosis[70]. Diagnosis can be achieved with a bedside Doppler ultrasound or with cross-sectional imaging or definitive angiography. Hepatic arterial thrombosis, as in the post-transplant setting, leads to irreversible hepatic ischemia. Portal and hepatic venous thrombosis can be managed expectantly with anticoagulation, although thrombectomy or radiological thrombolysis has also been demonstrated to be effective [71]. Postoperative perihepatic collections and abscesses contribute to and exacerbate SIRS and sepsis and need to be stringently looked for and drained with interventional imaging.

Cardiovascular hemodynamic aspects

Fluid resuscitation therapy is goal-directed to maintain adequate tissue perfusion in the context of excessive capillary leakage. Excessive inotropic support can contribute towards hepatic ischemia as discussed earlier. Reduced systemic vascular index leads to peripheral pooling, fluid extravasation, and tissue edema.

Acute kidney injury (AKI) is a common feature of PHLF whereas excessive hydration can lead to pulmonary edema and acute respiratory distress syndrome. Impaired renal function is followed by an increase in total body water, which again cause derangements in electrolytes such as hyponatremia. Use of diuretics is frequently followed by hypokalemia. Other electrolyte disturbances can be caused by hyperaldosteronism from failure of hormone breakdown, uremia related to the renal impairment, and hypophosphatemia associated with hepatic regeneration. A careful and timely adherence to readily available standard replacement scales is recommended to maintain electrolyte homeostasis.

Pulmonary complications such as acute lung injury(ALI) or acute respiratory distress syndrome(ARDS) are detrimental to the prognosis of patients with PHLF[14]. Early

intubation and use of ventilator support is promoted by current ARDS guidelines. However, prolonged use of increased positive end-expiratory pressure may worsen hepatic congestion, leading to portal hypertension, development of ascites and impaired liver regeneration.

Renal and metabolic derangement

Continuous hemofiltration or venovenous hemofiltration(CVVHF) is frequently necessary for patients with ALF and PHLF for the management of acute kidney injury and fluid overloading. Given the multifactorial nature of acute kidney injury in patients with PHLF, renal replacement therapy is challenging. Hypoperfusion, diuretics and vasoactive drugs, and contrast imaging studies may all contribute to an ongoing renal insult in this group of patients. When necessary, early commencement of renal replacement therapy(RRT) is indicated. Continuous RRT is better than intermittent application but there is no evidence that high volume RRT is significantly better than standard rate [72].

Hypoglycemia is encountered in some patients with PHLF and is due to an impaired hepatic gluconeogenesis and hyperinsulinemia, combined with reduced glycogen stores in the remaining liver. Administration of glucose by enteral or parenteral route as tolerated, is necessary. Continuous monitoring of the glycemic status is important. Of note, persistent hypoglycemia is regarded as a poor prognostic factor [73].

Management of neurological complications

Cerebral edema and hepatic encephalopathy are common in ALF as are levels of elevated serum ammonia. Raised intracranial pressure is the cause of death in nearly 15% of patients[74]. Elevated serum ammonia levels are associated with cerebral herniation and are predictive of mortality[75]. CVVHF also has the added benefit of achieving ammonia

clearance. The rate of CVVHF also correlates with the amount of ammonia clearance although it is unclear whether this specifically contributes towards improved survival[72]. Lactulose has been routinely used for the management of hepatic encephalopathy (HE) although current literature would suggest little evidence that it improves outcomes [76]. It can be poorly tolerated, can cause excessive GI disturbances and diarrhea which may potentially worsen the dehydration, AKI, and encephalopathy. Albumin has also been used in the treatment of HE alone or combination with lactulose with varying evidence of its efficacy [77]. Rifaximin is a broad-spectrum, minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract is equally effective against both gram-positive and negative cocci as well as anaerobes and has been used for the management of HE. A large randomized trial showed a clear benefit in maintaining remission and preventing hospitalization from HE [78]. A meta-analysis also confirms that antibiotics such as Rifaximin are better than disaccharides for the overall management of HE [76]. However, their role in specific management of HE related to PHLF hasn't been investigated. As a rule, grade 1-2 HE which is usually associated only with minimal cerebral edema can be managed expectantly. However, grade 3-4 HE is associated with significant cerebral edema with potential for tentorial herniation and needs the patient to be intubated and ventilated with specific measures such as hypothermia and administration of hypertonic saline. Routine use of hyperventilation and steroids is not beneficial [65].

Coagulopathy and bleeding

Coagulopathy is invariably present in patients with PHLF and is indolent and frequently associated with thrombocytopenia, leaving the patient at risk of hemorrhagic complications. It is well known that chronically low levels of platelets are well tolerated and there is no role for routine platelet or fresh frozen plasma transfusion unless a therapeutic procedure is planned or the patient develops active bleeding[79]. Apart from coagulopathy, other factors that

contribute to higher incidence of GI bleeding include mechanical ventilation, renal failure, sepsis, and shock. Several studies clearly indicate benefit of stress ulcer prophylaxis with H_2-receptor antagonists(H_2RA) or proton pump inhibitors(PPIs), however the mortality remains unaffected [80].

Infectious complications and sepsis

Postoperative perihepatic collections and abscesses contribute to and exacerbate systemic inflammatory response syndrome(SIRS)and sepsis and need to be stringently looked for and drained with interventional imaging. Repeat blood cultures should be obtained, to enable goal-directed antimicrobial therapy. SIRS is encountered in over half the patients with ALF and is accompanied by both gram-positive and gram-negative bacteremia [74]. Outcomes worsen with the number of organ system failures, and septic shock in patients with ALF is invariably fatal. Although there is no definitive role for postoperative antibiotic prophylaxis after liver resection, it improves outcomes for established ALF and by extension, likely for PHLF too. Broad-spectrum antibiotic therapy must be instituted as soon as possible. Fungal infections have worse outcomes than bacterial ones and there may be a role for anti-fungal prophylaxis although there is no definite evidence of its therapeutic role[74].

Drugs used in the management of PHLF

N-acetylcysteine(NAC) has long been used in management of ALF for its role as a cytoprotective agent. Although routinely used as a drug aiding recovery from paracetamol overdose and thereby minimizing the need for liver transplantation, less is known about its role in minimizing PHLF in patients undergoing major liver resection. Its potential benefit is based on the assumption that NAC has a protective effect on the remnant liver via its mechanism in influencing the ischemia-reperfusion injury (IRI) pathway. Although many

centers routinely use NAC postoperatively in patents deemed to be at high risk of developing PHLF, very little data are available to even draw any conclusive evidence for its benefit or otherwise [81].

In an experimental rat model of small-for-size transplant, perioperative use of somatostatin improved graft survival [82] whilst in a human study, strict perioperative glycaemic control resulted in improvement in liver dysfunction and postoperative complications [83]. However, none of these studies specifically dealt either with PHLF or mortality after liver resections.

Specific management of liver failure

The ultimate organ-specific management in PHLF and ALF in general would be liver support systems. Ideally, any artificial liver support should cover the whole range of liver function, including detoxification, synthesis, excretion, metabolic and regulatory functions. However, in practice, it is only the detoxification and excretory functions that need to be artificially supported since some of the synthetic and metabolic functions can potentially be managed medically. Over the last few years, many artificial and bio-artificial therapies have been attempted as discussed below.

Artificial liver support – extra-corporal liver support devices (ELSD)

The main aim of any artificial device or treatment is to take over some of the vital liver functions until native liver has sufficiently regenerated to hold its own, or, in case of irreversible failure, to act as a bridge towards definitive treatment in form of liver transplantation[14, 84, 85].

Principally, the ELSD can be subclassified in two types: 1) *Bioartificial type,* which is based on the use of living cells (porcine or human-derived) loaded in an extra-corporal bioreactor. Outside clinical trials, currently, no bioartificial system is available for clinically use[86]. 2) *Artificial liver support types*, where blood purification of protein-bound substances is achieved by various mechanical devices. Early ones included the molecular adsorbent recirculation system (MARS®)(Gambro, Lund Sweden) [87] and the single-pass albumin dialysis(SPAD)[88]. Further improvements included introduction of the fractionated plasma separation and adsorption(FPSA) system by Falkenhagen et al. in 1999[89]. Based on the combination of the FPSA method and high-flux hemodialysis of the blood, the Prometheus® system (Fresenius Medical Care, Bad Homburg, Germany) as an extracorporeal detoxification system was introduced[90].

A systematic review concluded that artificial and bioartificial liver (BAL) support systems might reduce mortality in acute-on-chronic liver failure (ACLF) compared with standard medical therapy, but not in patients with acute liver failure(ALF) [91]. Less than a decade later, Strutchfield and coworkers came to the opposite conclusion in their systematic review and meta-analysis that extra-corporal liver support systems appeared to improve survival in ALF, but not in those with ACLF[92].

It is unknown whether these outcomes in patients with medical liver failure could be extrapolated to those who have sustained PHLF. Moreover, patients with PHLF comprise a heterogeneous group of patients, treated for a variety of malignant and benign causes[93]. In a recent systematic review, Sparrelid et al concluded that early MARS treatment is both safe and feasible in patients with PHLF[94]. However, before MARS can be recommended as standard therapy for this group of patients, further prospective studies are warranted [94].

In a recent national population-based study, Wiesman and coworkers [95] report on a stable use of extracorporeal liver support between 2007–2015 in Germany. Interestingly

since 2012, ECLS therapy was used more often in cardiosurgical patients than in those with liver dysfunction[95]. Unfortunately, no specific information on ECLS related to PHLF was provided in this study.

Plasma exchange seems to be a valuable approach for patients with ALF and ACLF[14, 96]. The level of evidence is strong for the use of high-volume plasma exchange in selected patients with ALF[96]. However, there are only a few anecdotal case-reports of salvage plasmapheresis in patients with PHLF[97].

In summary therefore, the use of ELSD in patients with liver failure is still not universally accepted and has been met with skeptical reluctance[98]. As an alternative form of therapy for acute liver failure, including PHLF, both cell transplantation, bioartificial liver devices, or bioengineered whole organ liver transplantation may add to the therapeutic repertoire. However, several concerns and obstacles need to be solved before widespread clinical implementation can take place[99, 100]. In particular, safety concerns, including zenozoonosis and tumorigenicity, have to be addressed before cell transplantation, bioartificial liver devices , and bioengineered livers may translate into clinical use for PHLF patients [99].

Liver transplant

Theoretically, the only definitive and potentially curative management of irreversible PHLF would be a salvage liver transplantation. To be considered for LT, these patients would have to satisfy the accepted criteria for transplantation for acute liver failure (ALF). Unless the original hepatectomy was performed for a benign cause, the only accepted indication would be for HCC. For the latter, the original resection needs to have been performed for patients who would have satisfied the Milan criteria[101]. Reports of salvage LT for PHLF are sporadic, however, they have been shown to be successful in a few series of patients. It is

clear, though, that short and long-term outcomes are somewhat inferior to LT performed for regular indications and the incidence of perioperative complications is also quite high [20, 93]. Moreover, it would be incredibly difficult to justify use of scarce donor organs for such 'extended' and uncommon indications. Living donor liver transplantation for PHLF would be even more controversial and ethically challenging due to the inherent danger of donor coercion, and also the potential harm of a healthy person for limited benefits to the recipient. However, it has shown acceptable outcomes in a small series of patients initially operated for HCC where all but one was within Milan criteria [102], but also in a national cohort of patients transplanted for various reasons of PHLF[93]. Finally, it would make theoretical sense to utilize auxiliary partial liver transplantation where the graft takes over the liver function until the native liver generates. However, we were unable to identify any documented reports where this technique has been successfully employed for management of PHLF.

Summary

PHLF is a rare and a lethal complication after liver resection. Its occurrence can potentially both be predicted and minimized preoperatively. Significant advances have been made in the recent years in the diagnostic workup of patients undergoing liver major liver resections. Working algorithms have provided a good guide towards both selection of the patient and the appropriate operation.

The mainstay of clinical management still remains early identification of PHLF and instituting general care of the critically ill patient with focus on organ support, sepsis control and providing the optimal environment for liver regeneration. The role of artificial liver support has remained disappointingly small and unfortunately, there are no new developments on the horizon. Hence, the best way of managing PHLF is minimizing or preventing its occurrence.

Authors' contributions

JAS proposed and designed the concept of this work. JAS and RD have both contributed to the literature search and reviewing of the pertinent literature in detail, and both authors have also contributed in providing and comparing the data presented. JAS made a manuscript draft, which was further developed and revised by both authors, and the final submitted manuscript was approved by both authors.

Disclosure of interest

The authors declare that they have no competing interests.

Funding

No funding

Acknowledgments

None

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