Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS)

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Background. *Posthepatectomy liver failure is a feared complication after hepatic resection and a major cause of perioperative mortality. There is currently no standardized definition of posthepatectomy liver failure that allows valid comparison of results from different studies and institutions. The aim of the current article was to propose a definition and grading of severity of posthepatectomy liver failure.*
Methods. *A literature search on posthepatectomy liver failure after hepatic resection was conducted. Based on the normal course of biochemical liver function tests after hepatic resection, a simple and easily applicable definition of posthepatectomy liver failure was developed by the International Study Group of Liver Surgery. Furthermore, a grading of severity is proposed based on the impact on patients' clinical management.*
Results. *No uniform definition of posthepatectomy liver failure has been established in the literature addressing hepatic surgery. Considering the normal postoperative course of serum bilirubin concentration and International Normalized Ratio, we propose defining posthepatectomy liver failure as the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5. The severity of posthepatectomy liver failure should be graded based on its impact on clinical management. Grade A posthepatectomy liver failure requires no change of the patient's clinical management. The clinical management of patients with grade B posthepatectomy liver failure deviates from the regular course but does not require invasive therapy. The need for invasive treatment defines grade C posthepatectomy liver failure.*
Conclusion. *The current definition of posthepatectomy liver failure is simple and easily applicable in clinical routine. This definition can be used in future studies to allow objective and accurate comparisons of operative interventions in the field of hepatic surgery. (Surgery 2011;149:713-24.)*

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Accepted for publication October 18, 2010.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2010.10.001

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LIVER RESECTION is used increasingly for the management of a variety of benign and malignant conditions.[1,2] These data have paralleled substantial advances in perioperative management and operative techniques that have improved the safety of, and extended the indications for, liver resection over the past 2 decades[3,4] Extended liver resections, liver resections in diseased liver or liver parenchyma affected by chemotherapy, and repeat or staged liver resections are being used to achieve curative resection and extend long-term survival. The resulting small functional remnant liver volumes and compromised liver function in these patients increase the risk for the development of posthepatectomy liver failure (PHLF). Despite the introduction of functional and imaging measures to assess preoperatively the size and function of the future liver remnant, as well as the use of portal vein embolization as a preventive intervention,[5,6] PHLF remains a major concern and has been shown to be a predominant cause of hepatectomy-related mortality.[3,7-10]

The incidence of PHLF in the literature varies between 1.2% and 32% partly as a result of differences in the studied patient populations and performed procedures.[7,8,11-16] An additional reason for the observed range might be the lack of a universally accepted definition of PHLF.[17,18] Because of the increasing relevance of PHLF and its impact on perioperative outcome, a uniform definition of this complication is needed to enable a valid comparison of results between different studies across multiple institutions and countries. To gain wide acceptance and application in clinical as well as scientific practice, such a definition needs to be easily applicable to a broad spectrum of patients. In an attempt to standardize the definition of major complications after liver resection, we propose a definition and severity of grading of PHLF.

MATERIALS AND METHODS

Literature search. An extensive search of the English literature was carried out within the Medline database. Studies on hepatic resection published within the past 5 years were reviewed to assess whether a standard definition of PHLF has been accepted already among hepatic surgeons. The literature search was carried out among 12 leading surgery journals: *Journal of the American College of Surgeons*, *American Journal of Surgery*, *The British Journal of Surgery*, *Annals of Surgery*, *Journal of Gastrointestinal Surgery*, *Archives of Surgery*, *Journal of Clinical Oncology*, *World Journal of Surgery*, *Langenbeck's Archives of Surgery*, *Surgery*, *Annals of Surgical Oncology*, and *Liver Transplantation*. The search terms included "liver/hepatic resection," "hepatectomy" in association with the following terms "liver/hepatic failure," "liver/hepatic insufficiency," "liver/hepatic dysfunction," "complications," "morbidity," and "mortality." Studies on patients who underwent hepatic resection that provided a definition of PHLF were eligible for inclusion. There were no restrictions regarding the indication for hepatectomy, the underlying status of the liver, or the applied abdominal access (ie, open or laparoscopic hepatectomy). Studies on liver failure after liver transplantation were excluded, as were studies on liver resection in children.

The literature search was conducted independently by 2 authors (N.R. and M.K.), who identified relevant studies and extracted the definitions provided. The retrieved abstracts were screened, and in case of potentially relevant studies, full articles were obtained for detailed evaluation. Any disagreements during the processes of selection, extraction, and assessment were resolved by discussion with a third author (J.W.).

Study group. From August 2008, drafts of the definition and severity grading of PHLF were sent to the members of an International Study Group of Liver Surgery (ISGLS) for a critical review. The revised versions of the definition were recirculated among all members for approval and further comments. The proposed definition and grading of PHLF was discussed in detail at a consensus conference during the annual meeting of the Australian and New Zealand Hepatic, Pancreatic and Biliary Association Inc (ANZHPBA) at the Sunshine Coast, Queensland, Australia in October 2008. The decision was made to base the proposed definition on actual patient data. In November 2009, a first revision of the manuscript was sent to the members of the ISGLS. After all comments were considered, a second revision of the manuscript was sent to the members of the study group

in February 2010. In March 2010, the manuscript was recirculated among the authors for final approval.

RESULTS

Terminology. The literature review revealed "liver/hepatic failure" and "liver/hepatic insufficiency" as the terms applied most commonly for the description of PHLF. Some authors used "dysfunction" and "failure" to grade the severity of PHLF. To illustrate that the reported liver failure developed as a complication of hepatic resection, some authors used the prefix "postresectional" or "postoperative." We propose to standardize the terminology of this complication by using the term "posthepatectomy liver failure."

Available definitions. The literature search yielded a total of 1,928 references. The review of studies on hepatic resection revealed many different definitions of PHLF. This finding confirms that, based on the recently published literature, currently there is no generally accepted and applied definition or grading of severity of PHLF. Qualitative definitions of PHLF included 1 or multiple symptoms of postoperative impairment of liver function, such as coagulopathy, hyperbilirubinemia, ascites, and encephalopathy.[17,18] Most frequently, PHLF was defined quantitatively on the basis of postoperative laboratory tests using various cut-off values of serum bilirubin concentration and international normalized ratio (INR) or prothrombin time/index. Some authors considered the development of clinical symptoms, such as encephalopathy and ascites, in combination with results from liver function tests for the diagnosis of PHLF (Table I).[19-64] Few studies provided a grading of PHLF,[20,28,40,55] and few studies aimed to define PHLF actually identified predictors of death caused by PHLF. Balzan et al[49] published a study in 2005 with the intention to standardize the definition of PHLF and predict ultimately patient mortality. Their analysis of 704 patients who underwent partial hepatectomy identified PHLF characterized by the combination of prothrombin time index <50% and serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on POD 5 to be a strong predictor of postoperative mortality.[49] Another study of 1,059 noncirrhotic patients by Mullen et al[15] was designed to provide a standard definition of PHLF in a population of patients with normal preoperative liver function. These authors found that a peak serum bilirubin concentration >7 mg/dL predicted strongly liver-related death and worse postoperative outcomes after major hepatectomy.[15] In contrast to the above definitions, Schindl et al[65] provided a classification for the severity of PHLF; their score included 4 parameters (total serum bilirubin concentration, prothrombin time, serum lactate concentration, and grade of encephalopathy) and classified PHLF into 4 grades of severity.

Consensus definition of posthepatectomy liver failure. An analysis of the normal postoperative course of biochemical liver tests after hepatectomy demonstrated that in most patients, serum bilirubin concentration and INR return to levels within the normal range on postoperative day 5, including patients with major resections.[66] Based on these data, we have defined PHLF as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5. Increased INR and hyperbilirubinemia are defined according to the normal range of cut-off levels of the local laboratory. This definition applies to patients with normal and abnormal preoperative liver function. To relate these changes to an insufficient functional capacity of the remnant liver, other obvious causes for the observed biochemical and clinical alterations, such as biliary obstruction, should be excluded. Importantly, in patients with preoperatively increased INR or increased serum bilirubin concentration, PHLF is defined by an increasing serum bilirubin concentration and increasing INR on or after postoperative day 5 compared with the values of the previous day. Furthermore, the need for clotting factors such as fresh frozen plasma (FFP) to maintain normal INR on or after postoperative day 5 in combination with hyperbilirubinemia is considered PHLF.

Grading of severity of posthepatectomy liver failure. PHLF may present as a transient, postoperative impairment of liver function that recovers as the liver regenerates and liver volume increases. In other cases, liver function can deteriorate to a potentially life-threatening condition. In addition to the previous definition for the diagnosis of PHLF, we recommend that a grading system is used to classify the severity of this complication. The parameters to be considered for the definition and grading of PHLF are displayed in Table II. A patient's PHLF is graded by the worst identified criteria (ie, by fulfilling at least 1 criterion of noninvasive or invasive intervention, patients are classified to have PHLF grade B and C, respectively).

Grade A posthepatectomy liver failure: Grade A PHLF represents a postoperative deterioration of

Table I. Applied definitions of posthepatectomy liver failure in studies on hepatic resection

Study	*Year*	n	*Definition*
Suda et al[19]	2009	111	Postoperative liver dysfunction was assessed in terms of postoperative hyperbilirubinemia and subsequent fatal outcome. Postoperative hyperbilirubinemia was defined as an increase in serum total bilirubin greater than 10 mg/dL, without a hemolytic or obstructive mechanism, within 2 weeks after surgery.
Zorzi et al[20]	2008	65	Hepatic dysfunction: Peak postoperative bilirubin level >3 mg/dL or a prothrombin time >18 s. Hepatic insufficiency: Peak postoperative bilirubin level >7 mg/dL.
Kawano et al[16]	2008	134	Patients with a maximum postoperative serum total bilirubin level >10 mg/dL.
Rahman et al[21]	2008	138	Empirical markers of liver failure on postoperative day 7, including persistent hyperbilirubinemia (serum bilirubin level >4.1 mg/dL, coagulopathy (INR >2.5, despite early attempted correction with clotting factors), abdominal ascites (drainage volumes >500 mL/day), and encephalopathy with hyperbilirubinemia, and exclusion of other acute confusional states.
Ercolani et al[22]	2008	1260	Transient jaundice with a bilirubin level >5 mg/dL associated with severe alteration of coagulation factors.
Reddy et al[23]	2008	96	Postoperative bilirubin >7.0 mg/dL.
Hemming et al[24]	2008	830	Requiring FFP to maintain an INR <2.0 after the first 48 h postresection, encephalopathy, ascites requiring paracentesis or diuretics longer than 2 weeks, or a rise in bilirubin >7 mg/dL. Use of an INR of 2.0 and bilirubin >7 mg/dL.
Nakano et al[25]	2008	90	Liver failure was defined by a prothrombin time index of less than 50% of normal in addition to serum bilirubin more than 50 μmol/L on postoperative day 5 or thereafter.
Harbrecht et al[26]	2008	80	Hepatic dysfunction was defined as a bilirubin ≥2 mg/dL.
Vigano et al[27]	2008	593	Liver dysfunction: both a prothrombin time index <50% and a serum bilirubin level >5 mg/dL for 3 or more consecutive days.
Torzilli et al[28]	2008	207	Liver failure was considered mild when the serum total bilirubin level ranged from 2 to 5 mg/dL for more than 3 days after surgery, medium when it ranged from 5 to 10 mg/dL for more than 3 days after surgery, and severe when it was above 10 mg/dL for more than 3 days after surgery.
Adam et al[29]	2007	151	Increase in the serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) and a decrease in prothrombin time index to <50%.
Gomez et al[30]	2007	386	Patients who developed signs of encephalopathy or became jaundiced, with coagulopathy after surgery, were considered to have developed liver failure.
Ribero et al[31]	2007	112	Peak postoperative bilirubin level >171 μmol/L (ie, 10 mg/dL) unrelated to biliary obstruction and/or clinically significant ascites or hepatic encephalopathy.
Ferrero et al[32]	2007	119	Liver dysfunction: prothrombin time index <50% and serum bilirubin level >5 mg/dL for 3 or more consecutive days.
McCormack et al[14]	2007	116	50-50 criteria at fifth postoperative day.
Pawlik et al[33]	2007	212	Peak postoperative bilirubin >6 mg/dL.
Mullen et al[15]	2007	1059	Postoperative peak bilirubin >7.0 mg/dL.
Dinant et al[12]	2007	46	Increased bilirubin plasma levels (>50 μmol/L; ie, 2.9 mg/dL), prolonged prothrombin time (>15 s), and increased plasma ammonia levels, combined with signs of hepatic encephalopathy or hepatorenal syndrome, requiring intensive care.
Thia et al[34]	2007	77	Hepatic decompensation: new onset of encephalopathy or ascites, increase in prothrombin time by >3 s of the preoperative level or an increase in bilirubin level to twice the normal upper limit (bilirubin reference range: 3–24 μmol/L; ie, 0.2–1.4 mg/dL) if initially normal, or twice the baseline level if initially abnormal.
Figueras et al[35]	2007	300	Prothrombin time index <50% of normal and/or by serum bilirubin >50 μmol/L on postoperative day 5 or thereafter and/or encephalopathy.

(*continued*)

Table I. (*continued*)

Study	*Year*	n	*Definition*
Pessaux et al[36]	2007	200	Simultaneous presence of a prothrombin time index <50% and a serum bilirubin level >50 μmol/L (2.9 mg/dL) on day 5 after surgery.
Taura et al[37]	2007	293	Hepatic insufficiency included rupture of esophageal varices or hepatic encephalopathy.
Truant et al[38]	2007	31	Prothrombin time index (expressed as a percentage of the normal level of prothrombin activity) <50% and total serum bilirubin level >50 μmol/L (ie, 2.9 mg/dL) after postoperative day 4.
Nagino et al[39]	2007	423	Serum total bilirubin concentration exceeding 10 mg/dL.
Menon et al[40]	2006	517	Hepatic dysfunction: Prothrombin time >18 s or serum bilirubin concentration >30 μmol/L (ie, 1.7 mg/dL). Hepatic failure: Persistently raised level of bilirubin >100 μmol/L (ie, 5.8 mg/dL), Prothrombin time >24 s (or requiring daily FFP), and rising levels of aminotransferase with associated encephalopathy.
Cucchetti et al[41]	2006	200	Postoperative irreversible liver failure: growing impairment of liver function after hepatectomy that led to patient death or required transplantation.
Benoist et al[42]	2006	305	Postoperative liver failure: Association of prothrombin time index <30% of normal and serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on postoperative day 5.
Sano et al[43]	2006	102	Hepatic failure: Serum total bilirubin concentration >10.0 mg/dL during the postoperative period.
Ogata et al[44]	2006	36	Liver failure was defined by a prothrombin time index of <50% (of normal) and serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on postoperative day 5.
Capussotti et al[45]	2006	126	Postoperative liver failure was defined as a serum bilirubin concentration greater than 5.0 mg/dL or a prothrombin time index of 50% or less, 3 days or more after operation.
Cucchetti et al[11]	2006	154	Irreversible liver failure: Growing impairment of liver function after resection that led to patient death or required transplantation.
Chen et al[46]	2006	118	Postoperative hepatic insufficiency: prothrombin time index <50% of normal and/or by serum total bilirubin >2.9 mg/dL and/or encephalopathy.
Azoulay et al[47]	2006	60	Postoperative liver insufficiency: total bilirubin concentration >90 μmol/L (ie, 5.3 mg/dL) or prothrombin time index was <30% of the normal level within 7 days of operation. Asterixis and alteration of consciousness not related to the effects of drugs were considered signs of liver failure, even when isolated.
Karoui et al[13]	2006	214	Liver failure: prothrombin time index <50% of normal and/or serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on postoperative day 5 or thereafter.
Ohwada et al[48]	2006	75	Any one of the following criteria: persistent hyperbilirubinaemia (total bilirubin level >5 mg/dL) for more than 5 days after surgery, refractory massive ascites or pleural effusion (>2000 mL/day) for more than 7 days after surgery, hyperammonemia greater than 150 mg/dL (normally <40 mg/dL) and hepatic encephalopathy.
Balzan et al[49]	2005	775	Prothrombin time index <50% and serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on postoperative day 5 (50-50 criteria).
Nagano et al[50]	2005	212	Liver failure: Total serum bilirubin concentration >10 mg/dL.
Figueras et al[51]	2005	80	Prothrombin time index of less than 50% of normal and/or by serum bilirubin more than 50 μmol/L on postoperative day 5 or thereafter and/or encephalopathy.
Azoulay et al[52]	2005	69	At least 2 of the following parameters: total bilirubin ≥60 μmol/L (ie, 3.5 mg/dL), prothrombin time index ≤30% of normal level, and massive ascites (abdominal drain output >500 mL per day during more than 3 days). Asterixis and alteration of consciousness after exclusion of drug effect were considered as signs of liver failure, even when isolated.
Choukér et al[53]	2005	75	Prothrombin time index values of less than 60% on the first postoperative day.
Kimura et al[54]	2004	64	Serum bilirubin level >240 μmol/L (ie, 14 mg/dL).

(*continued*)

Table I. (*continued*)

Study	*Year*	n	*Definition*
Lodge et al[55]	2005	38	Hepatic dysfunction: Prothrombin time over 18 s or serum bilirubin concentration greater than 30 μmol/L. Hepatic failure: Persistently raised level of bilirubin >100 μmol/L (ie, 5.8 mg/dL), prothrombin time greater than 24 s (needing daily support with FFP), and increasing levels of aminotransferase with associated encephalopathy.
Vauthey et al[56]	2004	127	Total bilirubin >10 mg/dL or an INR >2.
Huo et al[57]	2004	241	Hepatic decompensation: sustained increment of the Child-Pugh score by 2 points or more (equivalent to Child-Pugh class B or C) during the follow-up period.
Hemming et al[58]	2004	22	Liver failure was defined arbitrarily as requiring FFP to maintain an INR >2.0 after the first 48 h postresection, encephalopathy, ascites requiring paracentesis or diuretics longer than 2 weeks, or an increase in bilirubin to 10 mg/dL or above that persisted longer than 10 days post resection.
Scatton et al[59]	2004	41	Severe hepatic dysfunction: encephalopathy, ascites (volume >500 mL/d), prothrombin time ratio lower than 50% of normal on day 5 or lower than 30% of normal at any moment, and bilirubin level greater than 50 μmol/L on day 5.
Kubo et al[60]	2004	251	Hepatic coma with hyperbilirubinemia (total serum bilirubin concentration >5 mg/dL for more than 5 days), intractable pleural effusion or ascites requiring use of diuretics or thoracocentesis, or abdominal paracentesis on 2 or more occasions or institution of continuous drainage, or variceal bleeding.
Parikh et al[61]	2003	108	Total serum bilirubin ≥10 mg/dL.
Lang et al[62]	2003	218	Appearance of hepatic encephalopathy, progressively worsening hyperbilirubinemia, and decreasing activity of blood coagulation as assessed by the prothrombin time.
Imamura et al[63]	2003	915	Serum bilirubin concentration greater than 5.0 mg/dL (>85 μmol/L), a prothrombin time rate of less than 50% for 3 or more consecutive days, or both.
Hemming et al[64]	2003	39	Development of encephalopathy, ascites requiring sustained diuretics or paracentesis, or coagulopathy unresponsive to vitamin K requiring FFP after the first 24 h postresection.

liver function that does not require a change in the patient's clinical management. This grade of PHLF is diagnosed based on deterioration from the preoperative baseline in routine laboratory tests indicating a postoperative impairment of liver function. These patients have no clinical symptoms deviating from a normal, expected postoperative course, do not require additional diagnostic evaluation, and can be managed on the regular ward.

Grade B posthepatectomy liver failure: Patients are diagnosed with grade B PHLF if there is a deviation from the regular, postoperative clinical pathway, but they can be managed without invasive treatment. Noninvasive treatment may include administration of FFP, albumin, daily diuretics, and noninvasive ventilation. Furthermore, the transfer to the intermediate or intensive care unit, which is related directly to the abnormal hepatic function, should be considered a criterion for grade B PHLF. These patients commonly need additional diagnostic evaluation, such as abdominal ultrasonography or computed tomography (CT), to exclude biliary obstruction and the presence of intra-abdominal fluid collection, respectively. If signs of infection (eg, leucocytosis and fever) are present, additional investigation by chest radiography and culture of sputum, blood, and urine should be entertained seriously. A brain CT may be considered to exclude other causes of altered mental status. Patients with grade B PHLF may present with clinically relevant ascites, weight gain, and mild respiratory insufficiency. Mild symptoms of encephalopathy may occur. These patients require management usually in an intermediate/intensive care unit; however, management on the regular ward by a team of experienced nursing staff may be justified.

Grade C posthepatectomy liver failure: Patients who develop PHLF requiring an invasive procedure are classified as having grade C PHLF. Invasive procedures include hemodialysis, intubation and mechanical ventilation, extracorporeal liver support, rescue hepatectomy, and transplantation. Furthermore, patients who require circulatory support (ie, vasoactive drugs) because of PHLF should be diagnosed with grade C PHLF, as

Table II. Consensus definition and severity grading of posthepatectomy liver failure (PHLF) by the International Study Group of Liver Surgery (ISGLS)

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, 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.

should patients who require glucose infusion for persistent hypoglycemia. Patients with grade C PHLF are in a critical clinical condition and should be monitored in an intensive care unit. The clinical presentation of these patients might be characterized by large volume ascites, generalized edema, hemodynamic instability, advanced respiratory failure, and encephalopathy. Furthermore, PHLF grade C patients are susceptible to infection, and prophylactic administration of antibiotics may be helpful, although subsequent evidence is required to support this course of action.

Table III summarizes the criteria for grading of PHLF.

Validation of the definition and grading of posthepatectomy liver failure. In a study on 835 patients who underwent liver resection at the Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Germany between January 2002 and January 2008, the clinical applicability of the proposed definition and grading of PHLF was assessed. The proposed definition could be applied in 576 patients in whom data on serum bilirubin concentration and INR on postoperative day 5 were available. A total of 65 patients (11%) fulfilled our criteria to diagnose PHLF. Of these, 5 patients (8%) had an uneventful postoperative hospital stay and were thus diagnosed with grade A PHLF. Some 47 patients (72%) had grade B PHLF, because they required a change in their clinical management without need for invasive therapy. Grade C PHLF was diagnosed in 13 patients (20%). The perioperative mortality of patients with PHLF grades A, B, and C was 0%, 12%, and 54%, respectively.[66]

DISCUSSION

The development of PHLF is a major cause of postoperative morbidity and mortality after elective hepatic resection.[3,7-10] The clinical relevance of PHLF within surgical practice has increased because extended resections are carried out more frequently, even in patients who have received potentially hepatotoxic systemic therapy. With smaller remnant liver volume and impaired functional capacity in some of these patients, there is an increased risk of PHLF.[15,49] Despite the growing relevance of PHLF in the postoperative management of patients with hepatic resection, there is no standardized definition of this complication. Our review of the hepatic surgery literature failed to identify a uniform definition of PHLF that has been accepted among hepatobiliary surgeons. In most studies, PHLF was defined by hyperbilirubinemia and/or impaired coagulation using various cut-off values of serum bilirubin concentration and/or INR (prothrombin time/index) at different postoperative time points. The cut-off values were chosen rather arbitrarily, whereas some studies applied the "50 – 50" criteria that is, the combination of prothrombin time index <50% and serum bilirubin >50 μmol/L (ie, 2.9 mg/dL) on postoperative day 5 as suggested by Balzan et al.[49] Alternatively, hyperbilirubinemia alone has been used as a definition of hepatic insufficiency to predict death from liver failure. Mullen et al[15] defined hepatic insufficiency as peak serum bilirubin >7 mg/dL using an analysis of receiver operating curves in 1,059 noncirrhotic patients who underwent major hepatectomy.[15] When the 50 – 50 criteria definition was tested, it was found less accurate

Table III. Criteria for grading of PHLF*

	Criteria for PHLF Grade A	*Criteria for PHLF Grade B*	*Criteria for PHLF Grade C*
Specific treatment	Not required	Fresh-frozen plasma Albumin Daily diuretics Noninvasive ventilation Transfer to intermediate/ intensive care unit	Transfer to the intensive care unit Circulatory support (vasoactive drugs) Need for glucose infusion Hemodialysis Intubation and mechanical ventilation Extracorporeal liver support Rescue hepatectomy/liver transplantation
Hepatic function	Adequate coagulation (INR <1.5) No neurological symptoms	Inadequate coagulation (INR ≥1.5 <2.0) Beginning of neurologic symptoms (ie, somnolence and confusion)	Inadequate coagulation (INR ≥2.0) Severe neurologic symptoms/ hepatic encephalopathy
Renal function	Adequate urine output (>0.5 mL/kg/h) BUN <150 mg/dL No symptoms of uremia	Inadequate urine output (≤0.5 ml/kg/h) BUN <150 mg/dL No symptoms of uremia	Renal dysfunction not manageable with diuretics BUN ≥150 mg/dL Symptoms of uremia
Pulmonary function	Arterial oxygen saturation >90% May have oxygen supply via nasal cannula or oxygen mask	Arterial oxygen saturation <90% despite oxygen supply via nasal cannula or oxygen mask	Severe refractory hypoxemia (arterial oxygen saturation ≤85% with high fraction of inspired oxygen)
Additional evaluation	Not required	Abdominal ultrasonography/CT Chest radiography Sputum, blood, urine cultures Brain CT	Abdominal ultrasonography/CT Chest radiography/CT Sputum, blood, urine cultures Brain CT ICP monitoring device

*The patient's PHLF is graded by the worst identified criteria in required treatment.
BUN, Blood urea nitrogen; *ICP*, intracranial pressure.

in predicting liver failure with sensitivity and specificity of 50% and 97%, respectively compared to peak serum bilirubin >7 mg/dL alone (sensitivity 93% and specificity 94%). Recently, a peak serum bilirubin of 7 mg/dL was validated to predict liver failure in patients with a small future liver remnant among 301 patients who underwent an extended right hepatectomy.[67]

The difficulty of assessing liver function postoperatively together with the limited availability of data regarding the kinetics of biochemical liver function tests after hepatic resection may explain why a standardized definition of PHLF has not yet been established. In a recent analysis that included patients who underwent a primary elective liver resection with no extrahepatic resection and who did not experience any complication postoperatively, the natural kinetics of biochemical liver function tests after hepatic resection have been described in a large cohort of patients.[66] This analysis revealed that median serum bilirubin concentration and INR return to levels within the normal range on postoperative day 5, even in patients who underwent major liver resection. Based on these data, we suggested that PHLF be defined as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR together with hyperbilirubinemia (according to the local laboratory) on or after postoperative day 5. It should be noted that the current definition does not provide general cut-off levels and does not use the patient's preoperative values to define increased INR and hyperbilirubinemia. These are, rather, determined using the normal range of INR and serum bilirubin concentration according to the local laboratory, and the current proposal is, therefore, unlikely to be subject to confounding because of various reference ranges at different laboratories.

Serum bilirubin concentration and INR (prothrombin time/index) are well-known measures of

hepatic function[68] and represent components of established liver function scores, such as the CTP (Child–Turcotte–Pugh) score and the model for end-stage liver disease (MELD) score.[69-72] Furthermore, the cut-off values for serum bilirubin concentration and INR (prothrombin time/index) have been identified as predictors of mortality from PHLF in previous studies.[15,49] These parameters were used in most individual definitions of PHLF as revealed by our literature search. Because serum bilirubin concentration and INR are, moreover, used commonly in clinical practice, they may allow the reliable and easy evaluation of hepatic function after hepatectomy.

Compared with previous definitions of surgical complications,[73-76] the current proposal was based on a large dataset of patients (ie, the actual course of serum bilirubin concentrations and INR after hepatic resection). A few reports have examined the postoperative course of biochemical liver tests after hepatectomy. Most of these studies, however, do not allow clear conclusions on the changes of these variables because they included patients with preoperative biliary obstruction as well as patients who developed complications and received clotting factors, respectively. Suc et al[77] described changes of biochemical and liver function tests after hepatic resection in a homogenous cohort of 33 patients who received no transfusion postoperatively and who had an uneventful postoperative course with normal residual liver on histologic analysis. These authors, however, did not report liver function tests for postoperative day 5 or relate these to the extent of resection at various time points during the postoperative period.[77] Based on a more recent analysis of the normal course of liver function tests after hepatic resection, we chose postoperative day 5 and beyond to define PHLF.[66] The biologic importance of this time point is confirmed by the recently proposed "50–50" criteria.[49] It should be noted that the current definition is applicable regardless of the extent of resection and patients' underlying liver disease. Although patients with extended resections and underlying liver abnormality are more likely to fulfill the criteria of PHLF even in cases of an uneventful postoperative course, this finding should be considered to reflect a transient insufficiency of the liver remnant to maintain function.

There have been previous attempts to assess and grade liver function after liver resection. The use of scoring systems, such as the CTP score and MELD score, to evaluate liver function *after* liver resection has been unclear. Preoperative use of the CTP score to predict postoperative prognosis after hepatic resection is established,[78] whereas its use postoperatively may be confounded by biliary obstruction, administration of FFP and albumin, lymphatic fistula, biliary leakage, and the impact of anesthesia. The MELD score is calculated by a formula including serum creatinine, serum bilirubin concentration, and INR. It has, however, been designed for risk assessment of patients with cirrhosis scheduled for transjugular intrahepatic portosystemic shunt and subsequently gained wide acceptance to prioritize candidates for liver transplantation.[71,72,79] The value of the MELD score is that this score is a preoperative risk index for patients scheduled for liver resection and is controversial,[11,78] as is its use as a postoperative measure of liver function,[41] because the postoperative changes in liver function tests were not considered. Recent studies aimed to standardize the definition of PHLF based on cut-off values for certain liver function tests, such as total serum bilirubin concentration and INR (prothrombin time index) as predictors of liver failure and mortality after hepatectomy.[15,49,65] These criteria may not detect all patients with PHLF and do not provide a grading of the severity of PHLF. They may still be useful for clinical decision making because they possibly enable the early identification of patients at high risk, and their use is recommended in addition to the proposed definition and grading of PHLF. Their use as predictor of outcome, however, requires subsequent validation within independent patient cohorts.

The current review of the hepatic surgery literature revealed that only few of the various definitions of PHLF provided a grading of severity. In these cases, the authors stratified the severity of PHLF using different cut-off values of serum bilirubin concentration and/or INR (prothrombin time index). In most cases, these values were chosen arbitrarily and do not necessarily reflect the patient's clinical condition. Indeed, the degree of PHLF may range from mild hepatic dysfunction to severe hepatic failure with clinical signs of systemic inflammatory response syndrome, hemodynamic instability, and ultimately, multiple organ failure. Similar to previous definitions of specific surgical complications and classifications of general operative complications, the severity of PHLF is best determined by its impact on patients' clinical management. It is defined less accurately by the degree of change in liver function tests, though these parameters are useful to diagnose this complication. Clearly, the proposed grading may be subject to variation

according to differences in treatment preferences and the lack of uniform guidelines for the treatment of PHLF and its associated sequelae.[18] We decided, however, to choose patient management to grade severity; we are convinced that the severity of organ dysfunction correlates well with the extent and invasiveness of therapy. Furthermore, the proposed grading of severity is easily applicable in daily practice as well as for the purpose of retrospective analyses and, thus, is likely to gain rapid acceptance among hepatobiliary surgeons. Using the current proposal, the development of PHLF was evaluated in a large cohort of patients who underwent liver resection.[66] Subsequent studies providing prospective validation of this proposed definition and grading of severity of PHLF are required.

In summary, the current proposal offers a simple, reproducible and generally applicable definition and grading of severity of PHLF. We suggest that this definition be used in future studies to standardize the reporting of this complication and, thus, enable more accurate comparisons between different studies involving hepatic resection.

REFERENCES

1. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol 2005;23:8490-9.
2. Weitz J, Blumgart LH, Fong Y, Jarnagin WR, D'Angelica M, Harrison LE, et al. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. Ann Surg 2005;241:269-76.
3. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698-708.
4. Rahbari NN, Wente MN, Schemmer P, Diener MK, Hoffmann K, Motschall E, et al. Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. Br J Surg 2008;95:424-32.
5. Mullin EJ, Metcalfe MS, Maddern GJ. How much liver resection is too much? Am J Surg 2005;190:87-97.
6. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49-57.
7. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999; 229:210-5.
8. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38-46.
9. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406.
10. Laurent C, Sa CA, Couderc P, Rullier E, Saric J. Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. Br J Surg 2003;90:1131-6.
11. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, La BG, et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006;12:966-71.
12. Dinant S, de GW, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. J Nucl Med 2007;48:685-92.
13. Karoui M, Penna C, min-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1-7.
14. McCormack L, Petrowsky H, Jochum W, Furrer K, Clavien PA. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case-control study. Ann Surg 2007;245:923-30.
15. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62.
16. Kawano Y, Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, et al. Short- and long-term outcomes after hepatic resection for hepatocellular carcinoma with concomitant esophageal varices in patients with cirrhosis. Ann Surg Oncol 2008;15: 1670-6.
17. Helling TS. Liver failure following partial hepatectomy. HPB (Oxford) 2006;8:165-74.
18. van den Broek MA, Damink SW, Dejong CH, Lang H, Malago M, Jalan R, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int 2008;28:767-80.
19. Suda K, Ohtsuka M, Ambiru S, Kimura F, Shimizu H, Yoshidome H, et al. Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies. Am J Surg 2009;197:752-8.
20. Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey JN. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. Ann Surg Oncol 2008;15:2765-72.
21. Rahman SH, Evans J, Toogood GJ, Lodge PA, Prasad KR. Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. Arch Surg 2008;143:247-53.
22. Ercolani G, Ravaioli M, Grazi GL, Cescon M, Del GM, Vetrone G, et al. Use of vascular clamping in hepatic surgery: lessons learned from 1260 liver resections. Arch Surg 2008; 143:380-7.
23. Reddy SK, Morse MA, Hurwitz HI, Bendell JC, Gan TJ, Hill SE, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg 2008;206:96-106.
24. Hemming AW, Reed AI, Fujita S, Zendejas I, Howard RJ, Kim RD. Role for extending hepatic resection using an aggressive approach to liver surgery. J Am Coll Surg 2008;206: 870-5.
25. Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008;247:118-24.
26. Harbrecht BG, Rosengart MR, Bukauskas K, Zenati MS, Marsh JW Jr, Geller DA. Assessment of transcutaneous

bilirubinometry in hospitalized adults. J Am Coll Surg 2008; 206:1129-36.
27. Vigano L, Ferrero A, Sgotto E, Tesoriere RL, Calgaro M, Capussotti L. Bile leak after hepatectomy: predictive factors of spontaneous healing. Am J Surg 2008;196:195-200.
28. Torzilli G, Donadon M, Marconi M, Botea F, Palmisano A, Del FD, et al. Systematic extended right posterior sectionectomy: a safe and effective alternative to right hepatectomy. Ann Surg 2008;247:603-11.
29. Adam R, Aloia T, Levi F, Wicherts DA, de Haas RJ, Paule B, et al. Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. J Clin Oncol 2007;25: 4593-602.
30. Gomez D, Malik HZ, Bonney GK, Wong V, Toogood GJ, Lodge JP, et al. Steatosis predicts postoperative morbidity following hepatic resection for colorectal metastasis. Br J Surg 2007;94:1395-402.
31. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386-94.
32. Ferrero A, Vigano L, Polastri R, Muratore A, Eminefendic H, Regge D, et al. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. World J Surg 2007;31:1643-51.
33. Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-8.
34. Thia TJ, Lui HF, Ooi LL, Chung YF, Chow PK, Cheow PC, et al. A study into the risk of exacerbation of chronic hepatitis B after liver resection for hepatocellular carcinoma. J Gastrointest Surg 2007;11:612-8.
35. Figueras J, Llado L, Miro M, Ramos E, Torras J, Fabregat J, et al. Application of fibrin glue sealant after hepatectomy does not seem justified: results of a randomized study in 300 patients. Ann Surg 2007;245:536-42.
36. Pessaux P, Regimbeau JM, Dondero F, Plasse M, Mantz J, Belghiti J. Randomized clinical trial evaluating the need for routine nasogastric decompression after elective hepatic resection. Br J Surg 2007;94:297-303.
37. Taura K, Ikai I, Hatano E, Yasuchika K, Nakajima A, Tada M, et al. Influence of coexisting cirrhosis on outcomes after partial hepatic resection for hepatocellular carcinoma fulfilling the Milan criteria: an analysis of 293 patients. Surgery 2007;142:685-94.
38. Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O, et al. Remnant liver volume to body weight ratio > or =0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg 2007;204:22-33.
39. Nagino M, Nishio H, Ebata T, Yokoyama Y, Igami T, Nimura Y. Intrahepatic cholangiojejunostomy following hepatobiliary resection. Br J Surg 2007;94:70-7.
40. Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. J Am Coll Surg 2006;203:677-83.
41. Cucchetti A, Ercolani G, Cescon M, Ravaioli M, Zanello M, Del GM, et al. Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease. J Am Coll Surg 2006; 203:670-6.
42. Benoist S, Salabert AS, Penna C, Karoui M, Julie C, Rougier P, et al. Portal triad clamping (TC) or hepatic vascular exclusion (VE) for major liver resection after prolonged neoadjuvant chemotherapy? A case-matched study in 60 patients. Surgery 2006;140:396-403.
43. Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg 2006;244:240-7.
44. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg 2006;93:1091-8.
45. Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. Br J Surg 2006;93: 685-9.
46. Chen XP, Zhang ZW, Zhang BX, Chen YF, Huang ZY, Zhang WG, et al. Modified technique of hepatic vascular exclusion: effect on blood loss during complex mesohepatectomy in hepatocellular carcinoma patients with cirrhosis. Langenbecks Arch Surg 2006;391:209-15.
47. Azoulay D, Lucidi V, Andreani P, Maggi U, Sebagh M, Ichai P, et al. Ischemic preconditioning for major liver resection under vascular exclusion of the liver preserving the caval flow: a randomized prospective study. J Am Coll Surg 2006;202: 203-11.
48. Ohwada S, Kawate S, Hamada K, Yamada T, Sunose Y, Tsutsumi H, et al. Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. Br J Surg 2006;93:339-46.
49. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-8; discussion.
50. Nagano Y, Nojiri K, Matsuo K, Tanaka K, Togo S, Ike H, et al. The impact of advanced age on hepatic resection of colorectal liver metastases. J Am Coll Surg 2005;201:511-6.
51. Figueras J, Llado L, Ruiz D, Ramos E, Busquets J, Rafecas A, et al. Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. Ann Surg 2005;241:582-90.
52. Azoulay D, Eshkenazy R, Andreani P, Castaing D, Adam R, Ichai P, et al. In situ hypothermic perfusion of the liver versus standard total vascular exclusion for complex liver resection. Ann Surg 2005;241:277-85.
53. Choukér A, Martignoni A, Schauer RJ, Dugas M, Schachtner T, Kaufmann I, et al. Alpha-gluthathione S-transferase as an early marker of hepatic ischemia/reperfusion injury after liver resection. World J Surg 2005;29:528-34.
54. Kimura F, Itoh H, Ambiru S, Shimizu H, Togawa A, Yoshidome H, et al. Circulating heat-shock protein 70 is associated with postoperative infection and organ dysfunction after liver resection. Am J Surg 2004;187:777-84.
55. Lodge JP, Menon KV, Fenwick SW, Prasad KR, Toogood GJ. In-contiguity and non-anatomical extension of right hepatic trisectionectomy for liver metastases. Br J Surg 2005;92:340-7.
56. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH, et al. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 2004;239:722-30.
57. Huo TI, Lui WY, Wu JC, Huang YH, King KL, Loong CC, et al. Deterioration of hepatic functional reserve in patients with hepatocellular carcinoma after resection: incidence, risk factors, and association with intrahepatic tumor recurrence. World J Surg 2004;28:258-62.

58. Hemming AW, Reed AI, Langham MR Jr, Fujita S, Howard RJ. Combined resection of the liver and inferior vena cava for hepatic malignancy. Ann Surg 2004;239:712-9.
59. Scatton O, Belghiti J, Dondero F, Goere D, Sommacale D, Plasse M, et al. Harvesting the middle hepatic vein with a right hepatectomy does not increase the risk for the donor. Liver Transpl 2004;10:71-6.
60. Kubo S, Tsukamoto T, Hirohashi K, Tanaka H, Shuto T, Takemura S, et al. Correlation between preoperative serum concentration of type IV collagen 7s domain and hepatic failure following resection of hepatocellular carcinoma. Ann Surg 2004;239:186-93.
61. Parikh AA, Gentner B, Wu TT, Curley SA, Ellis LM, Vauthey JN. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. J Gastrointest Surg 2003;7:1082-8.
62. Lang BH, Poon RT, Fan ST, Wong J. Perioperative and long-term outcome of major hepatic resection for small solitary hepatocellular carcinoma in patients with cirrhosis. Arch Surg 2003;138:1207-13.
63. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198-206.
64. Hemming AW, Reed AI, Howard RJ, Fujita S, Hochwald SN, Caridi JG, et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg 2003;237:686-91.
65. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289-96.
66. Reissfelder C, Rahbari NN, Koch M, Kofler B, Sutedja N, Elbers H, et al. Postoperative course and clinical significance of biochemical blood tests following hepatic resection. Br J Surg; In press.
67. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg. In press.
68. Bismuth H, Houssin D, Mazmanian G. Postoperative liver insufficiency: prevention and management. World J Surg 1983;7:505-10.
69. Child CGI, Turcotte JG. Surgery and portal hypertension. In: Child CGI, editor. The liver and portal hypertension. Philadelphia (Pa): Saunders; 1964. p. 50-8.
70. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-9.
71. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-71.
72. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33:464-70.
73. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
74. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142:761-8.
75. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-5.
76. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147:339-51.
77. Suc B, Panis Y, Belghiti J, Fekete F. Natural history' of hepatectomy. Br J Surg 1992;79:39-42.
78. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006;243: 373-9.
79. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002;8:851-8.