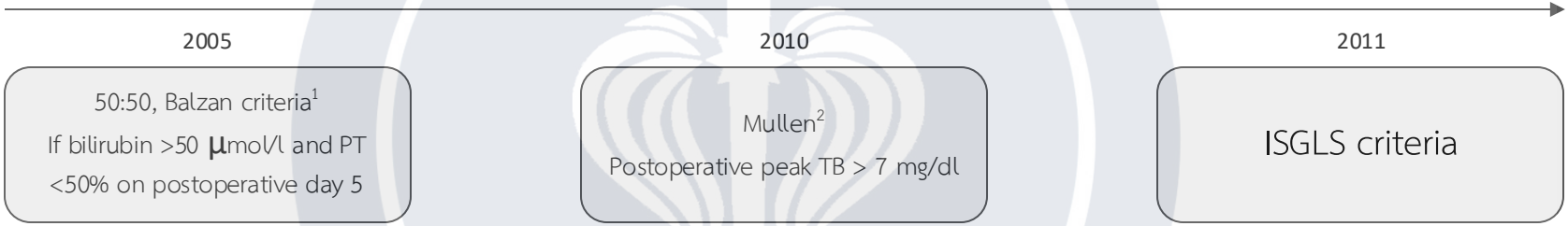
Mahidol University
Faculty of Medicine Ramathibodi Hospital

Post hepatectomy liver failure

F Ativitch Asavachaisuvikom
HPB unit, Department of Surgery, Ramathibodi hospital

Introduction

Definition



[1]Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D et al. The "50–50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005;242:824–828

Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S et al. Hepatic insufficiency and mortality in 1059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007;204:854–862

Definition

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

Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011 May;149(5):713-24. doi: 10.1016/j.surg.2010.10.001. Epub 2011 Jan 14. PMID: 21236455.

Grading

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 managment

Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011 May;149(5):713-24. doi: 10.1016/j.surg.2010.10.001. Epub 2011 Jan 14. PMID: 21236455.

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

BUN, Blood urea nitrogen; *ICP*, intracranial pressure.

Epidemiology

Using the ISGLS criteria, the incidence of PHLF in recent publications, incidence 9 - 20 % in western cohorts at tertiary centres

National Surgical Quality Improvement Program database in the USA, under 5%(Both Major and Minor hepatectomy)

In Thailand ;

KKU reported incidence 38.5%(Only major hepatectomy in CCA)

Ramathibodi reported incidence 3.4%

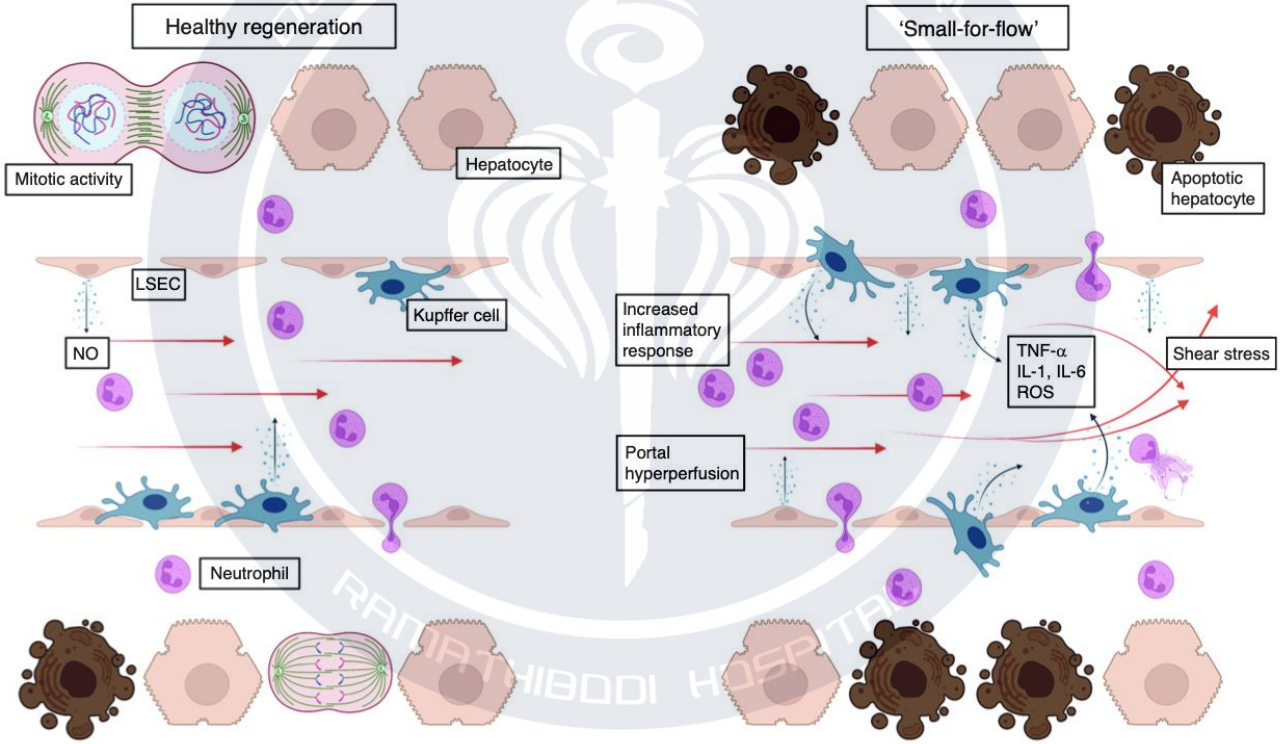
Sultana A, Brooke-Smith M, Ullah S, Figueras J, Rees M, Vauthey JN et al. Prospective evaluation of the International Study Group for Liver Surgery definition of post hepatectomy liver failure after liver resection: an international multicentre study. *HPB (Oxford)* 2018;20:462–469.

Starlinger P, Ubl DS, Hackl H, Starlinger J, Nagorney DM, Smoot RL et al. Combined APRI/ALBI score to predict mortality after hepatic resection. *BJS Open* 2021

Kriengkrai W, Somjaiyong B, Titapun A, Wongsem P. Predictive Factors for Post-Hepatectomy Liver Failure in Patients with Cholangiocarcinoma. Asian Pac J Cancer Prev. 2023 Feb 1;24(2):575-580. doi: 10.31557/APJCP.2023.24.2.575. PMID: 36853307; PMCID: PMC10162621.

Vassanasiri, W., Rungsakulkij, N., Suragul, W. et al. Early postoperative serum aspartate aminotransferase for prediction of post-hepatectomy liver failure. Perioper Med 11, 51 (2022). https://doi.org/10.1186/s13741-022-00283-y

Pathophysiology



Sparrelid E, Olthof PB, Dasari BVM, Erdmann JI, Santol J, Starlinger P, Gilg S. Current evidence on posthepatectomy liver failure: comprehensive review. BJS Open. 2022 Nov 2;6(6):zrac142.doi: 10.1093/bjsopen/zrac142. PMID: 36415029; PMCID: PMC9681670.

Patient factors	Male sex
	Advanced age (>65 years)
	Obesity (BMI >30) and malnutrition
	Diabetes and other comorbidity
Factors related to hepatic parenchyma	Pre-existing liver disease • cirrhosis • fibrosis • steatosis Pre-operative chemotherapy effects • sinusoidal congestion • steatohepatitis Cholestasis—hyperbilirubinemia Cholangitis
Surgery related	Intraoperative blood loss (>1200 ml) Intraoperative transfusion Extended liver resection (>4 segments) Prolonged inflow occlusion("Pringle") Prolonged operating time (>240 min) Need for associated resection (e.g. vascular, colon) or vascular reconstruction Hypotension
Postoperative factors	Postoperative hemorrhage Intra-abdominal infections Major postoperative complications

Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) - Recent advances in prevention and clinical management. Eur J Surg Oncol. 2021 Feb;47(2):216-224. doi: 10.1016/j.ejso.2020.09.001. Epub 2020 Sep 10. PMID: 32943278.

Prevention

Preoperative

- Liver assessment
- Nutritional support
- Preoperative measurement of spleen thickness

Intraoperative

- Avoid necessary dissection of hepatoduodenal ligament
- Intermittent pringle
- Avoid blood transfusion
- Two-stage resection

Postoperative

- Early detection and treatment of complication such as bleeding, bile leak and intraabdominal infection

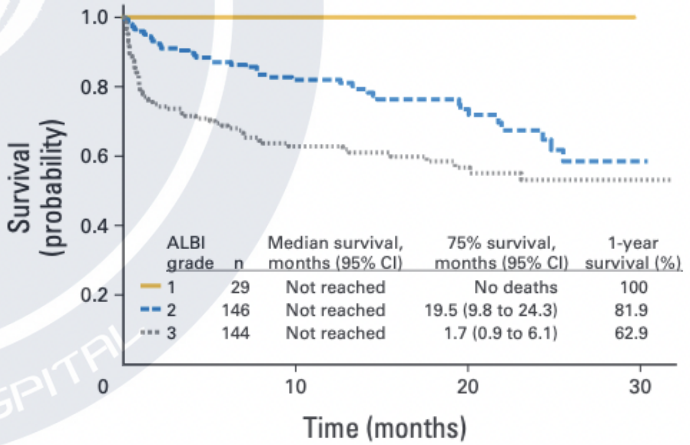
Preoperative management

Liver assessment

- Biochemical evaluation of liver function test
- Volumetric assessment
- Function of liver volume
- Radiological assessment of fractional and regional liver function

Biochemical evaluation

- Child Pugh score
- MELD score(Model for End-stage Liver Disease)
- Albumin-Bilirubin index(ALBI)
  - Predicting outcomes after liver resection f
    - Linear predictor(xb) = (log_{10}bilirubin(umol/L) x 0.6
      - Grade 1 : xb <= -2.60
      - Grade 2 : -2.60 < xb <= -1.39
      - Grade 3 : xb >= -1.39

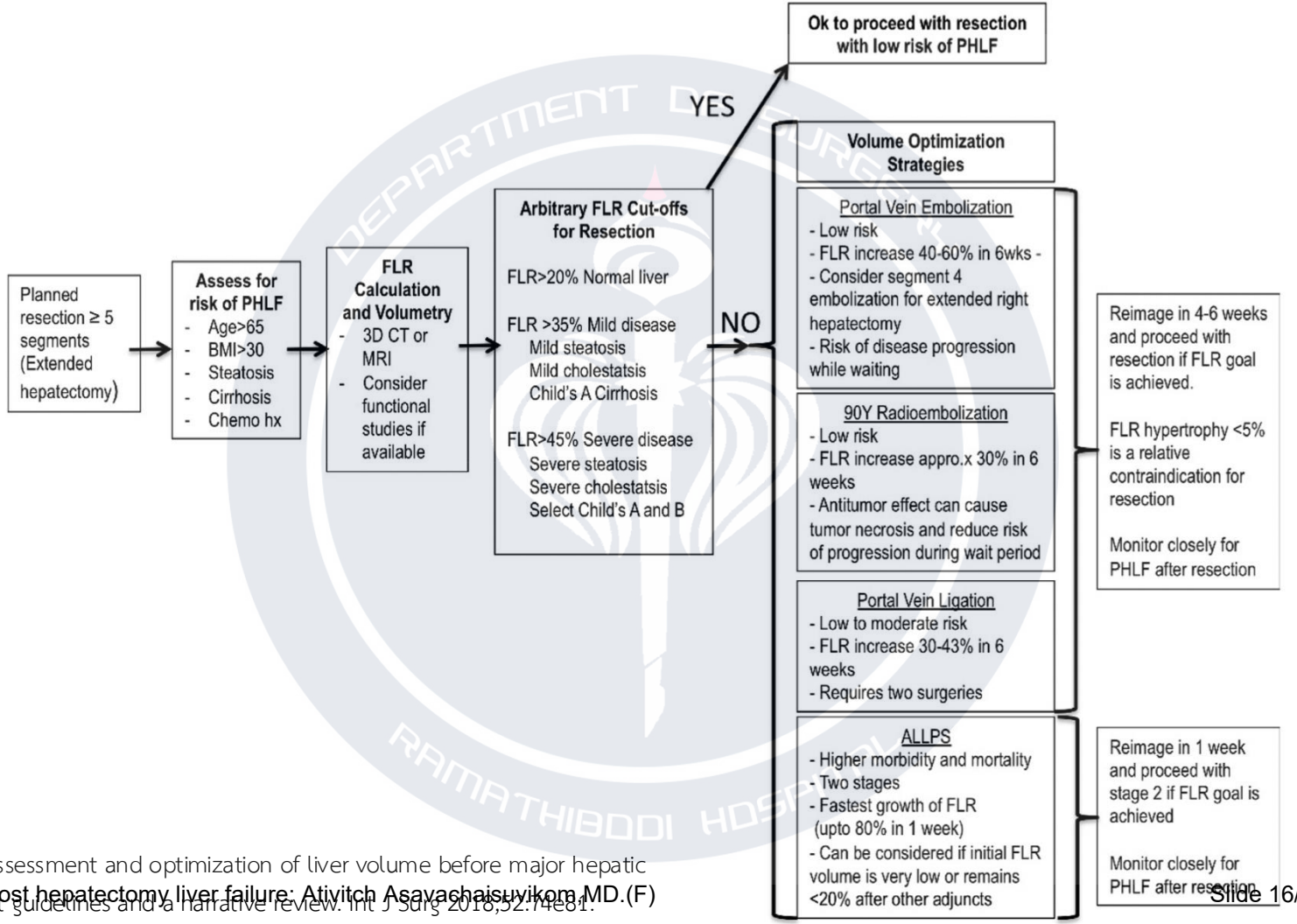


Johnson PJ, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550e8.

Volumetric assessment

- Future liver remnant volume (%FLR) by computer tomography(CT)
  - 20-25 % in normal liver
  - 30% in pre-existing chemotherapy treatment
  - 40% in liver cirrhosis

Kokudo T, et al. Assessment of preoperative liver function for surgical decision making in patients with hepatocellular carcinoma. Liver Cancer 2019;8:447e56.
Khan AS, et al. Assessment and optimization of liver volume before major hepatic resection: current guidelines and a narrative review. Int J Surg 2018;52:74e81.



Khan AS, et al. Assessment and optimization of liver volume before major hepatic resection: current guidelines and a narrative review. Int J Surg 2018;52:74e81.

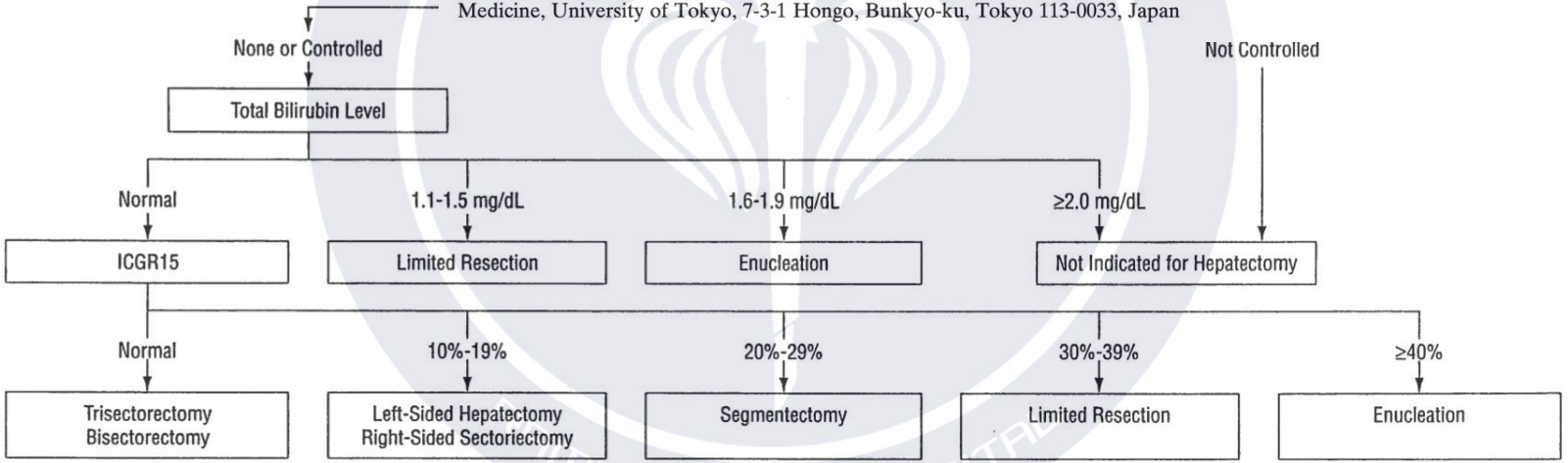
Function of liver volume

- ICG R-15

Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test

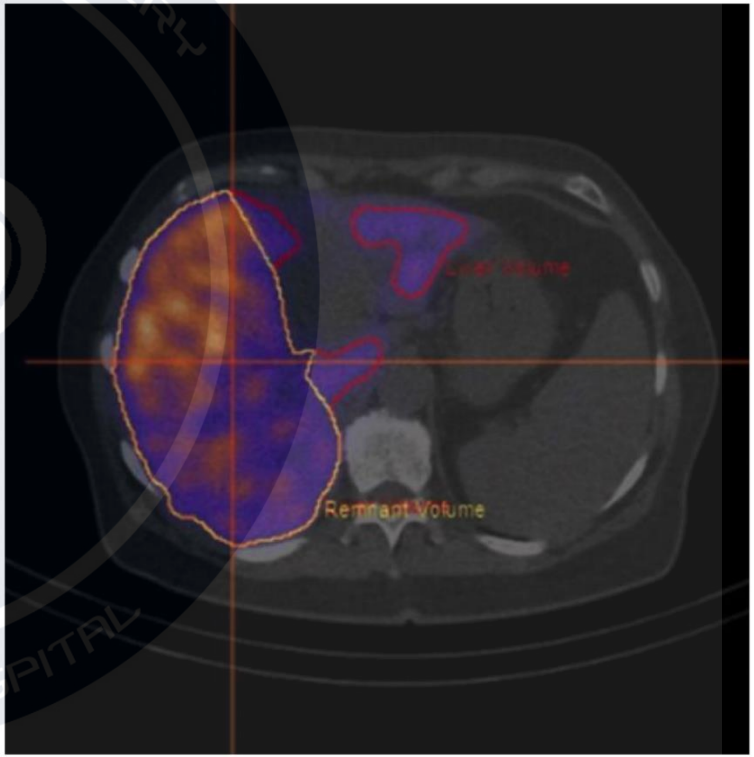
HIROSHI IMAMURA, KEIJI SANO, YASUHIKO SUGAWARA, NORIHIKO KOKUDO, and MASATOSHI MAKUUCHI

Division of Hepato-Biliary-Pancreatic Surgery and Artificial Organ and Transplantation, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan



Radiological assessment of fractional and regional liver function

- 99 m Tc-mebrofenin scintigraphy
- Gd-EOB-DTPA enhanced magnetic resonance imaging(EOB-MRI)



Haimerl M, et al. Gd-EOB-DTPA-enhanced T1 relaxometry for assessment of liver function determined by real-time (13)C-methacetin breath test. Eur Radiol 2018;28:3591e600.

Intraoperative management

Intraoperative managements

- Pringle maneuvers
  - Prefer intermittent pringle
- Intraoperative blood loss
  - Intraoperative blood loss of more than 1200 ml and the need for perioperative blood transfusion are considered risk factors for PHLF
  - Kept minimum blood loss; low CVP, CUSA or energy devices
- Flow modulation
  - Splenectomy and splenic artery ligation
    - living-donor liver transplantation; however, its role in extended hepatectomies is only described in animal studies

Melendez J, Ferri E, Zwillman M, Fischer M, DeMatteo R, Leung D *et al.* Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. *J Am Coll Surg* 2001; **192**:47–53

Wang H, Ikegami T, Harada N, Yoshizumi T, Soejima Y, Uchiyama H et al. Optimal changes in portal hemodynamics induced by splenectomy during living donor liver transplantation. Surg Today 2015;45:979–985

Intraoperative managements

- Pharmacological intervention of portal venous flow
  - Intraoperative bolus dose of somatostatin
    - In animal trials, marked reduction in portal venous flow and pressure and attenuation of liver injury
    - RCT : SOMAPROTECT01(ongoing trial)
- N-acetylcysteine administration
  - RCT : Failed to demonstrate benefit[1]
- Intraoperative steroid
  - Potent anti-inflammatory drugs that modulate inflammatory and anti-inflammatory pathways
  - Methylprednisolone 500 mg before induction or up to 90 min before surgery was used demonstrated favorable operative changes[2]

only small 5 RCT
Small number of cirrhosis patients

[1]Grendar J, Ouellet JF, McKay A, Sutherland FR, Bathe OF, Ball CG et al. Effect of N-acetylcysteine on liver recovery after resection: a randomized clinical trial. J Surg Oncol 2016;114: 446–450

[2]Richardson AJ, Laurence JM, Lam VW. Use of pre-operative steroids in liver resection: a systematic review and meta-analysis. HPB (Oxford) 2014;16:12–19

Postoperative management

Intraoperative managements

- Early detection and treatment of complication
  - Bleeding
  - Bile leak
  - Infection
    - Intraabdominal infection
    - UTI
    - Pleural effusion
    - Catheter related infection

Treatment

Identify and treat causes

- Vascular inflow/outflow obstruction
- Infections : Post operative perihepatic collections and abscesses, Bile leaks
- Inadequate liver remnants

GOALS : Liver regeneration

Ascites controlled

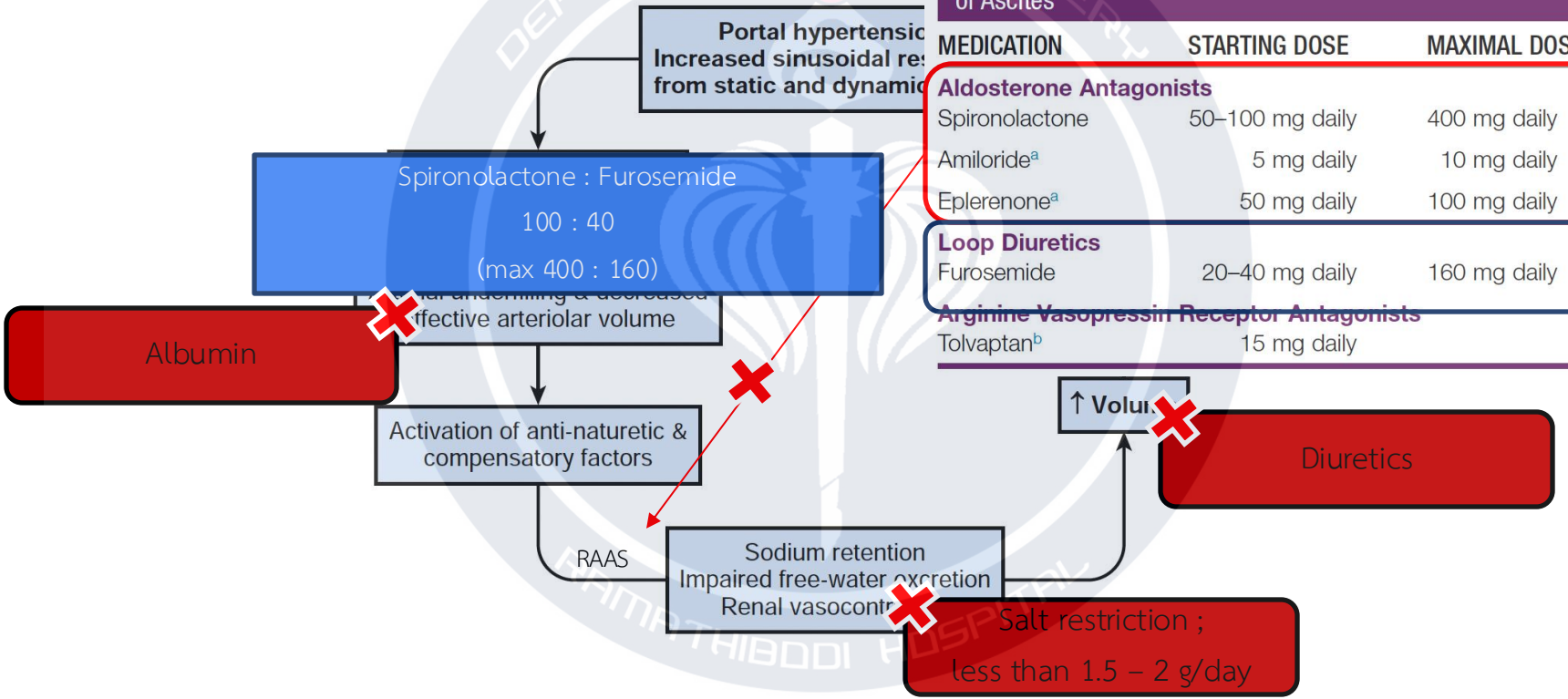


TABLE 79.1 Diuretics and Dosages Used in the Management of Ascites

MEDICATION	STARTING DOSE	MAXIMAL DOSE
Aldosterone Antagonists		
Spironolactone	50–100 mg daily	400 mg daily
Amiloride[a]	5 mg daily	10 mg daily
Eplerenone[a]	50 mg daily	100 mg daily
Loop Diuretics		
Furosemide	20–40 mg daily	160 mg daily
Arginine Vasopressin Receptor Antagonists		
Tolvaptan[b]	15 mg daily	

Jin S, Fu Q, Wuyun G, Wuyun T. Management of post-hepatectomy complications. World J Gastroenterol. 2013;19:7983–7991.

Kevin M. Korenblat, Blumgart's surgery, p.1061-1068, Management of ascites in cirrhosis and portal hypertension

Ascites controlled

- Refractory ascites
  - Ascites that persists despite dietary sodium restriction and high-dose diuretics (spironolactone 400 mg per day; furosemide 160 mg per day)
  - Treatment
    - Abdominal paracentesis
    - TIPS
    - Peritoneovenous shunt
    - Liver transplantation

Kevin M. Rokenblat, Blumgart's surgery, p.1061-1068, Management of ascites in cirrhosis and portal hypertension

Cardiovascular hemodynamic aspects

- Fluid resuscitation therapy is goal-directed
- Keep urine output > 0.5 ml/kg/hr
- Not excessive fluid hydration
    - Pulmonary edema
    - Multiple electrolyte imbalance such as hyponatremia

Pulmonary complications

- Pulmonary complications such as acute lung injury(ALI) or acute respiratory distress syndrome(ARDS) are detrimental to the prognosis of patients with PHLF.
- Protective ventilation with low Tidal volume(6 ml/kg) is recommend
    - However, prolonged use of increased PEEP may worsen hepatic congestion, leading to portal hypertension, development of ascites and impaired liver regeneration.

Kandiah PA, et al. Emerging strategies for the treatment of patients with acute hepatic failure. Curr Opin Crit Care 2016;22:142e51

Renal and Metabolic complication

- 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
- Hypoglycemia
  - due to an impaired hepatic gluconeogenesis and hyperinsulinemia, combined with reduced glycogen stores in the remaining liver.
  - Continuous monitoring of the glycemic status is important.

Kang ZQ, et al. Effects of perioperative tight glycemic control on post- operative outcomes: a meta-analysis. Endocr Connect 2018;7:R316e27.

Neurological complication

- Cerebral edema and hepatic encephalopathy are common in ALF as are levels of elevated serum ammonia
- Predictive of mortality[1]
- Management
  - Lactulose has been routinely used for the management of hepatic encephalopathy (HE)[2]
  - CVVHF also has the added benefit of achieving ammonia clearance

[1]Clemmesen JO, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29: 648e53.
[2]Als-Nielsen B, et al. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046.

Coagulation and bleeding

- Coagulopathy and thrombocytopenia
- ***No role for routine*** platelet or fresh frozen plasma transfusion unless a therapeutic procedure is planned or the patient develops active bleeding

Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med 2000;162:347e51.

Infectious complication

- No definitive role for postoperative antibiotic prophylaxis after liver resection
- But if establish ALF
  - Broad-spectrum antibiotic therapy must be instituted as soon as possible

Rolando N, et al. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32:734e9.

Specific management

- Artificial liver support extracorporal liver support devices (ELSD)
- Liver transplant
    - Theoretically, the only definitive and potentially curative management of irreversible PHLF
    - Might be feasible and safe for PHLF after surgical resection of benign liver tumours or HCC within established criteria.

Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) - Recent advances in prevention and clinical management. Eur J Surg Oncol. 2021 Feb;47(2):216-224.

Roberta Angelico, Leandro Siragusa, Matteo Serenari, Irene Scalera, Emanuele Kauffman, Quirino Lai, Alessandro Vitale, Rescue liver transplantation after post-hepatectomy acute liver failure: A systematic review and pooled analysis, Transplantation Reviews, Volume 37, Issue 3, 2023,

Take home message

- Post hepatectomy liver failure is serious complication
- Grading : ISGLS 2011
- Prevention
  - Preoperative : Liver assessment, Nutrition
  - Intraoperative : Diminish blood loss, Intermittent pringle
  - Postoperative : Early detect complication

Take home message

- Treatment
  - CVS : Goal directed therapy
  - RS : Low TV
  - GI : Restrict Na < 1.5-2 g/day, Combine diuretic, Albumin
  - KUB : Keep urine output > 0.5 ml/kg/day, CVVH may be indicated
  - Metabolic : Monitor glucose level
  - Neuro : If HE was present, lactulose has been used
  - Infection : No routine prolong prophylaxis antibiotic, but if ALF was present > Board spectrum antibiotic was indicated

Take home message

- Specific treatment
  - Artificial liver support e extra-corporal liver support devices (ELSD)
  - Rescue liver transplantation

Thank you