

# Clinical, Laboratory, and Perioperative Management Characteristics in Liver Resection Cases in Fatmawati General Hospital

Nikko Darnindro\*, Jessica Marsigit\*, Adianto Nugroho\*\*, Anggraini Permata Sari\*, M. Azhari Taufik\*\*\*, Dieby Adrisyel\*\*\*\*, Elizabeth Yasmine Wardoyo\*, Apriliana Ratnaningrum\*\*, Danny Darmawan\*

\*Department of Internal Medicine, Fatmawati General Hospital, Jakarta

\*\*Department of Digestive Surgery, Fatmawati General Hospital, Jakarta

\*\*\*Department of Anesthesiology and Intensive Therapy, Fatmawati General Hospital, Jakarta

\*\*\*\*Department of Radiology, Fatmawati General Hospital, Jakarta

## Corresponding author:

Nikko Darnindro. Department of Internal Medicine, Fatmawati General Hospital. Jalan Raya RS Fatmawati Cilandak Barat Jakarta Indonesia. Phone: 021-7657822. E-mail: nikkodarnindro@gmail.com

## ABSTRACT

**Background:** Liver resection has been associated with high morbidity and mortality. Improvements in surgical, anesthetic techniques, and multidisciplinary collaborations, can reduce post-surgery complications and mortality. This study aims to provide an overview of the perioperative conditions and the treatments after liver resection.

**Method:** A retrospective study of liver resection surgery between 2019-2020 at Fatmawati Hospital.

**Results:** Of the 11 patients, mean age was 49.7 years, with 63.6% being female and mean BMI was 22 kg/m<sup>2</sup>, hypertension and diabetes mellitus were found in 18.2% and 18.2% of patients respectively. HBsAg reactive was detected in 36.3%. Based on pathology, HCC was found in 54.5%, while 18.2% were metastatic adenocarcinoma. Postoperative hyperglycemia was observed in 90.9%. Increase in AST and ALT > 3 upper limit normal were found in 90% and 72.7% of patients. Mean AST and ALT were 408.3 U/L and 246.18 U/L. Mean urine production at 8-, 16-, 24-, and 48-hours post-operative were 757, 1624, 1880 and 1930 cc. Urine production ≤ 500 cc in the first 8 hours was detected in 44.4% of patients, and elevated creatinine levels >50% post-operative occurred at 11.1%, 22.2%, 22.2% at 16, 24, and 48 hours post-op. Renal support therapy was given to 5 of the 11 patients. D-Dimer levels were increased in all patients.

**Conclusion:** Adequate fluid monitoring and metabolic disorders control such as glucose levels, acute kidney injury, coagulation disorders, and bleeding are important things that need to be considered in the perioperative management of liver resection.

**Keywords:** liver resection, management perioperative, multidiscipline

## ABSTRAK

**Latar belakang:** Reseksi hati merupakan tindakan pembedahan yang terkait dengan tingginya morbiditas dan mortalitas. Dengan kemajuan teknik pembedahan, anestesi, serta kolaborasi multidisiplin, komplikasi pasca-pembedahan serta mortalitas akan menurun. Studi ini bertujuan untuk memberikan gambaran mengenai kondisi perioperatif pada pasien setelah reseksi hati dan tatalaksana yang diberikan.

**Metode:** Sebuah studi retrospektif, terdiri dari 11 pasien yang menjalani reseksi hati antara tahun 2019-2020 di RS Fatmawati.

**Hasil:** Dari 11 pasien, rerata usia adalah 49,7 tahun dengan 63,6% adalah perempuan. Rerata IMT adalah 22 kg/m<sup>2</sup>, hipertensi dan diabetes mellitus ditemukan masing-masing 18,2%. HBsAg reaktif terdeteksi pada 36,3% pasien. Berdasarkan patologi, karsinoma sel hati (KSH) ditemukan pada 54,5% pasien dan 18,2% adenokarsinoma metastatik. Hiperglikemia pascaoperasi ditemukan pada 90,9% dari pasien. Peningkatan AST dan ALT >3x batas atas ditemukan pada 90% dan 72,7%, dengan rerata level AST adalah 408,3 U/L dan ALT 246,18 U/L. Setelah pembedahan, rerata produksi urin pada jam ke-8, -16, -24, dan -48 adalah 757 cc, 1624 cc, 1880 cc, dan 1930 cc. Pasien yang memiliki produksi urin ≤ 500 cc pada 8 jam pertama sebanyak 44,4%, peningkatan level kreatinin >50% dari data pre-operasi terjadi pada 11,1%, 22,2%, 22,2% pada jam ke-16, -24, dan -48 pasca operasi. Terapi pendukung ginjal diberikan pada 5 dari 11 pasien. Level D-Dimer meningkat pada semua pasien.

**Simpulan:** Pemantauan adekuasi cairan serta gangguan metabolik seperti kadar glukosa, gagal ginjal akut, gangguan koagulasi, pendarahan, serta pencegahan kegagalan hati merupakan faktor-faktor penting yang perlu diperhatikan dalam tatalaksana manajemen perioperatif pada reseksi hati.

**Kata kunci:** reseksi hati, tatalaksana perioperatif, multidisiplin

## INTRODUCTION

Liver malignancy is the 6<sup>th</sup> and 5<sup>th</sup> most common cancer in the world and Indonesia, respectively. Liver malignancy is the 4<sup>th</sup> cause of death in Indonesia, both in women and men.<sup>1</sup> The most common primary liver malignancies consist of two types, namely hepatocellular carcinoma (75-85%) and intrahepatic cholangiocarcinoma (10-15%). Risk factors for hepatocellular carcinoma (HCC) include infection of hepatitis B, hepatitis C, hepatic cirrhosis, alcohol consumption, aflatoxin consumption, being a smoker, obesity, and non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD). The diagnosis of HCC was made based on the INA-ASL 2017 which needs to fulfill at least 2 of the 3 criteria below: the presence of underlying liver disease (hepatitis B, hepatitis C, or hepatic cirrhosis), the presence of positive liver laboratory tests (AFP ≥ 200 ng/mL or PIVKA-II ≥ 40 mAU/mL), as well as the presence of supporting radiological features, which are hypervascularization in the arterial phase and wash-out in the venous phase based on computerized tomography scan (CT scan) or multiphase magnetic resonance imaging (MRI).<sup>2</sup> One of the mandatory criteria is having a typical radiological picture. Stages in HCC can be grouped based on Barcelona clinic liver cancer (BCLC) assessment which consists of liver function degree by Child-Pugh classification, performance status by Eastern Cooperative Oncology Group (ECOG) assessment and liver tumor extension.<sup>2,3</sup> Meanwhile, intrahepatic cholangiocarcinoma is a collection of cancers in the biliary duct with an incidence of 2.1 per 100,000 population in western countries. The risk factors of intrahepatic cholangiocarcinoma are

similar to HCC, which include cirrhosis, chronic viral hepatitis, alcohol consumption, diabetes, and obesity. To establish a diagnosis, other than based on a pathological diagnosis, it can be made by supporting examinations such as positron emission tomography scan (PET-scan) and Ca 19-9 examination.<sup>4</sup>

The management of primary liver malignancies such as HCC and intrahepatic cholangiocarcinoma depends on several factors, including the degree of liver function as assessed by Child-Pugh classification, vascular invasion, extrahepatic spread, number of nodules, and nodule size. One of the most important things that need to be considered before deciding to do a liver resection is the assessment of the remaining liver after resection. Liver resection is the main treatment for HCC with Child-Pugh A/B without vascular invasion and extrahepatic spread, without portal hypertension, and with nodules ≤ 3. This can be done by measuring the retention rate of indo-cyanine green at 15 minutes. In 1970, the mortality rate after liver resection could reach 20%. Along with advances in surgical techniques and perioperative management, this mortality rate can be reduced. However, several complications after liver resection can still occur, including post-hepatectomy liver failure with a prevalence ranging from 0.7-35%, acute kidney failure with a prevalence of 0.9-15.1%, and coagulation disorders with a prevalence reaching 45%.<sup>5,6</sup> Strict monitoring of fluid balance in and out of the body along with early detection of complications after liver resection needs special attention to reduce mortality and provide better perioperative management.

Liver resection surgery is one of the curative measures to treat liver malignancies, both primary and secondary, both malignant and non-malignant. However,

as previously explained, there are many things that need to be known in the preparation and handling or even prevention of possible complications. This study was conducted to evaluate the perioperative condition of patients undergoing liver resection surgery. By obtaining clinical characteristics, laboratory results, and treatment, provide better management could be addressed.

**METHODS**

This study was conducted retrospectively from the medical records, of 11 patients who underwent liver resection surgery in 2019-2020 at Fatmawati General Hospital. Demographic data, initial diagnosis, anatomic pathology diagnosis, postoperative laboratory results, and administered treatment were taken from medical records.

**RESULTS**

Of the 11 patients, the mean age was 49.7 years, with 63.6% being female. Based on preoperative clinical characteristics, the mean body mass index (BMI) was 22 kg/m<sup>2</sup> with hypertension and diabetes mellitus found in 18.2% of patients, respectively. 36.3% of patients were hepatitis B surface antigen (HbsAg) reactive and none had reactive results of anti-HCV. Based on the anatomic pathology results, the diagnosis of HCC was found in 54.5% of patients, whereas 18.2% were diagnosed as metastatic adenocarcinoma, 1 patient had gallbladder adenocarcinoma and 1 patient had hepatolithiasis. Demographic data are presented in Table 1.

The mean of hemoglobin before and after surgery was 12 g/L and 9.8 g/L, respectively. Postoperative hyperglycemia was observed in 90.9% of patients and was controlled using insulin. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 3 upper normal limits (ULN) were found in 90% and 72.7% of patients with an average AST level of 408.3 U/L and ALT 246.18 U/L. After surgery, the average urine output at 8-, 16-, 24-, and 48-hours after were 757 cc, 1624 cc, 1880 cc, and 1930 cc, respectively. 44.4% of patients had a urine output of 500 cc in the first 8 hours, whereas in serial creatinine levels evaluation, an increase in creatinine levels > 50% of preoperative data was found in 11.1%, 22.2%, 22.2% in 16-, 24-, and 48-hours after the surgery.

Renal replacement therapy through hemodialysis or continuous renal replacement therapy (CRRT) was given to 5 out of 11 patients and was given between

16-48 hours postoperatively, indicated due to decreased urine production or increased creatinine levels. The mean D-Dimer level was 5,469 (2,350-11,822) and was increased in all patients (Table 2). Heparin was administered 8 hours after surgery with titrating dose, starting at 5,000 units per 24 hours accompanied by close monitoring of activated partial thromboplastin time (aPTT) and D-Dimer levels.

**DISCUSSION**

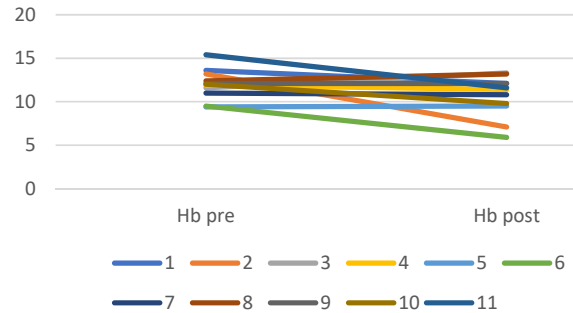


Figure 1. Hemoglobin levels pre-post resection

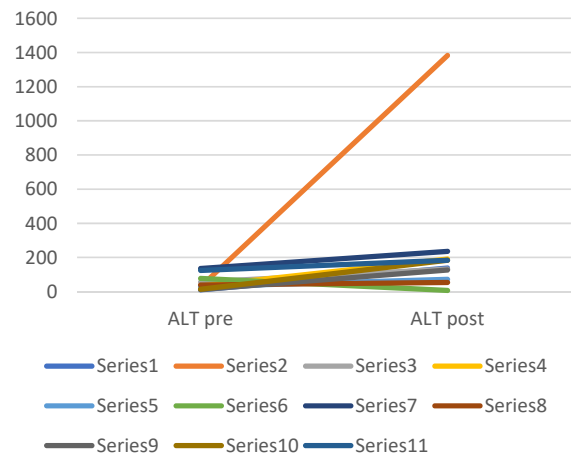


Figure 2. ALT levels during monitoring

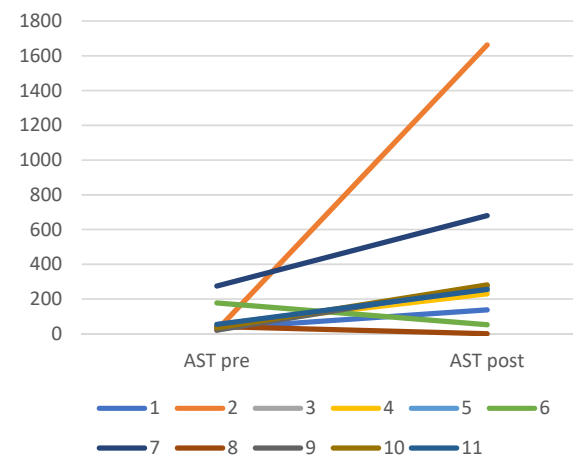


Figure 3. AST levels during monitoring

Table 1. Demographic data

Patient	Sex	Age (years old)	BMI (kg/m <sup>2</sup> )	Hypertension	Diabetes mellitus	HBsAg (reactive/not)	Anti-HCV (reactive/not)	Malignancy	Anatomic pathology results	Pre-surgery Hb (g/L)	Post-surgery Hb (g/L)	Pre-surgery RBG (mg/dL)	Post-surgery RBG (mg/dL)
1	Female	78	22.4	No	No	Not	Not	Yes	Gallbladder Adenoca	13.60	12.10	80	192
2	Female	44	29.3	Yes	Yes	Not	Not	Yes	HCC	13.20	7.10	99	305
3	Male	47	26.3	No	No	Reactive	Not	Yes	HCC	11.60	13.30	119	153
4	Male	55	30.8	No	No	Reactive	Not	Yes	HCC	11.90	11.40	105	191
5	Female	49	24.9	No	Yes	Reactive	Not	Yes	HCC	9.40	9.50	346	160
6	Male	49	20.2	No	No	Not	Not	Yes	HCC	9.50	5.90	180	150
7	Female	49	21.2	No	No	Reactive	Not	Yes	HCC	11.00	10.80	120	210
8	Female	49	18.5	Yes	No	Not	Not	No	Hepatolithiasis	12.40	13.20	128	269
9	Female	50	17.6	No	No	Not	Not	Yes	Metastasis Adenoca	12.10	12.10	86	187
10	Female	32	21.9	No	No	Not	Not	Yes	Metastasis Adenoca	12	9.8	144	209
11	Male	44	25.5	No	No	Not	Not	No	Benign Adenoca	15.4	11.6	97	131

BMI: body mass index, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, Hb: haemoglobin, RBG: random blood glucose, HCC: hepatocellular carcinoma

Table 2. Laboratory results during monitoring

Patient	Sex	Pre-surgery albumin (g/dL)	Pre-surgery AST (U/L)	Post-surgery AST (U/L)	Pre-surgery ALT (U/L)	Post-surgery ALT (U/L)	Pre-surgery Bilirubin (g/dL)	Post-surgery Bilirubin (g/dL)	Pre-surgery Procalcitonin (ng/mL)	Pre-surgery Kr (mg/dL)	Kr 0 - hour post-surgery	Kr 8 - hour post-surgery	Kr 16 - hour post-surgery	Kr 24 - hour post-surgery	Kr 48 - hour post-surgery	Post-surgery D-Dimer (ng/mL)	Renal therapy
1	Female	4.00	31	137	10	138	3.00	3.00	0.25	0.60	0.80	0.60	0.70	N/A	N/A	7,668	No
2	Female	4.50	20	1,663	29	1,383	0.00	0.00	29.40	0.90	1.20	N/A	2.00	2.20	2.60	5,232	Yes
3	Male	4.20	52	249	56	132	0.00	0.00	0.53	1.00	1.10	N/A	N/A	0.80	0.90	11,822	No
4	Male	3.50	49	230	32	191	1.60	1.60	0.88	0.90	0.70	0.90	0.90	0.90	N/A	2,350	No
5	Female	2.80	42	260	30	72	1.10	1.10	5.41	0.50	0.50	N/A	N/A	0.60	0.60	2,410	Yes
6	Male	2.80	177	52	77	7	N/A	N/A	3.21	0.90	1.70	0.90	0.90	0.90	N/A	4,715	Yes
7	Female	3.60	275	680	136	236	N/A	N/A	1.37	0.60	0.50	0.50	0.70	0.60	N/A	N/A	No
8	Female	3.60	41	N/A	39	54	1.00	1.00	4.30	1.20	1.20	1.20	1.20	1.20	2.30	3,748	No
9	Female	3.90	20	276	12	127	0.00	0.00	22.30	0.50	0.50	0.30	1.30	2.10	N/A	4,538	Yes
10	Female	3.20	34	281	14	184	0.48	0.48	5.64	0.30	0.50	0.50	0.50	0.50	0.40	7,613	Yes
11	Male	4.00	54	255	124	184	0.00	0.00	32.00	1.90	1.00	0.80	0.80	0.80	0.80	4,509	No

AST: aspartate aminotransferase, ALT: alanine aminotransferase

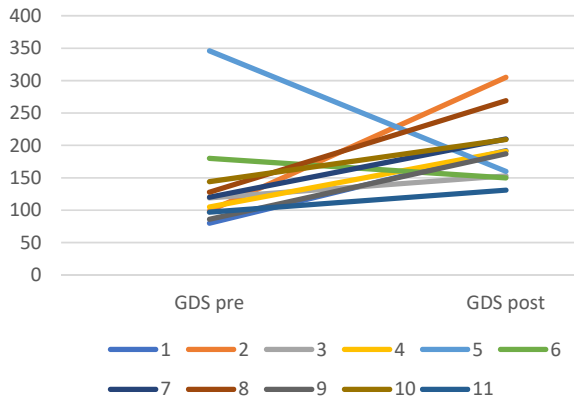


Figure 4. Random blood glucose level pre-post resection

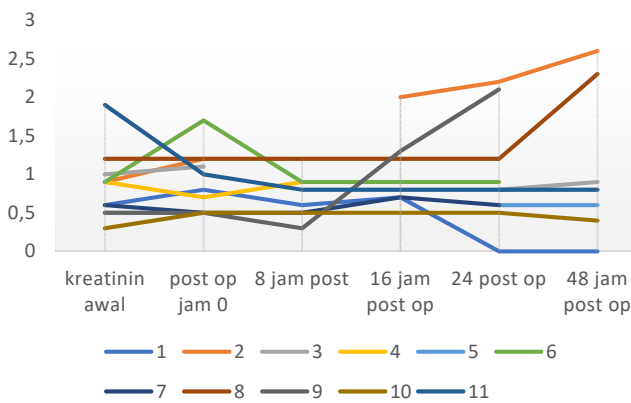


Figure 5. Creatinine levels during monitoring

Liver resection is one of the definitive treatment options for patients with primary liver malignancy with the following criteria: Child-Pugh A/B without vascular invasion and extrahepatic spread, and with nodules  $\leq 3$ . In patients with Child-Pugh A or without hepatic cirrhosis, complications after liver resection are less common than in patients with liver cirrhosis or Child-Pugh B classification. Patients with Child-Pugh A may live with 75% of the total liver capacity with 6 liver segments.<sup>7</sup> In the above case series, 9 of 11 patients underwent liver resection with liver malignancy as the indication, either primary or metastatic malignancy. Liver cell carcinoma was found in 6 of 11 cases, and 2 cases were metastases from primary tumors elsewhere. There are several complications after liver resection, including post-hepatectomy liver failure, acute kidney failure, and coagulation disorders.<sup>5,6</sup> Complications of liver failure is one of the severe post-resection complications which may cause death, the incidence varies depending on the condition of the liver before resection, as well as the underlying pathology.

In the perioperative management of liver resection, to reduce the risk of post-resection liver failure, several indicators can be used to assess the feasibility. In addition to using the ASA score to assess the feasibility of anesthesia, the Child-Pugh classification, and the

model of end-stage liver disease (MELD) score can be used in the assessment. Patients with a Child-Pugh score  $< 8$  have good tolerance and acceptable risk, whereas patients with a MELD score of 10-15 have a high risk of surgery, and if the score exceeds 15, surgery should be postponed. In individuals with normal liver parenchyma conditions, the remaining liver volume based on a CT-Scan examination of 25-30% after resection is considered sufficient for the body's metabolic needs and preventing liver failure. Laboratory tests such as INR, bilirubin, albumin, platelets, and also indocyanine green clearance can be used to predict post-resection liver function.<sup>8</sup>

Post hepatectomy liver failure is defined as a decrease in liver function including its synthesis, excretion, and detoxification processes, which is characterized by an increase in INR (increased prothrombin time of more than 50% from baseline), an increase in transaminase enzymes (more than 1,000 IU/mL), and hyperbilirubinemia. (more than 2 mg/dL).<sup>9,10</sup> In the case series above, an increase in ALT levels (SGPT)  $> 3$  times the upper limit of normal was found in 8 of 11 patients, and 1 patient had ALT levels (SGPT)  $> 1000$  IU/mL. Liver failure after hepatectomy may occur up to day 5 after the procedure and increases the risk of death by up to 59%.<sup>9</sup>

Liver failure can occur because in partial liver resection there will be an increase in portal vein pressure due to decreased vascular volume and increased portal flow per gram of tissue. This will increase the pressure on the vascular endothelium so that factors such as nitric oxide (NO) will be released by the sinusoidal cells. NO will reduce the synthesis of S-adenosyl methionine (SAM) so that there will be an increase in the expression of cyclin D1 and D2 which increases the production of hepatocyte growth factors (HGFs).<sup>5</sup> However, not only does the production of HGFs synthesis increase, but the pressure on the vascular endothelium also causes necrosis and tissue damage in hepatocytes triggering the release of inflammatory factors such as Interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>5</sup> Furthermore, liver resection can cause Kupffer cell dysregulation and Prostaglandin E2 (PGE2) hyposecretion, which further reduces hepatocyte protection against apoptosis.<sup>5</sup> Risk factors for liver failure after hepatectomy include advanced age, metabolic factors, sepsis, renal insufficiency, hepatic steatosis, degree of liver fibrosis, amount of bleeding during surgery, surgical technique, and residual liver volume.<sup>5,11</sup>

Acute renal failure (ARF) after liver resection was

defined as an increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours or 50% from baseline. ARF after liver resection consists of 3 stages, namely: stage 1 where there is an increase in creatinine  $\geq 0.3$  mg/dL or an increase in creatinine 1.5-2 times; stage 2 where there is an increase in serum creatinine 2-3 times the initial value; and stage 3 where there is an increase in serum creatinine  $\geq 4.0$  mg/dL or in need of renal replacement therapy.<sup>6</sup> In the perioperative management of liver resection patients at Fatmawati General Hospital, periodic monitoring of creatinine levels and urine production were carried out to detect early acute kidney disorders. In the case series above, 5 patients underwent renal replacement therapy either with hemodialysis or with continuous renal replacement therapy (CRRT). Apart from bleeding during surgery, post-hepatectomy liver failure also contributes to acute renal failure and hepatorenal syndrome (HRS). HRS is defined as a decrease in glomerular filtration rate and renal plasma flow in the absence of other causes of renal failure. An increase in portal venous pressure due to liver failure after hepatectomy causes splanchnic arterial vasodilation, thereby reducing vascular resistance and causing renal artery hypovolemia.<sup>12</sup> This situation increases the activity of the renin-angiotensin-aldosterone system, resulting in vasoconstriction of the renal arteries and decreasing the glomerular filtration rate. There are two types of HRS, particularly HRS-AKI, which can occur in patients with chronic kidney disease grade 1 and 2, characterized by increased creatinine levels. While the other type is HRS-non-AKI which must meet the HRS criteria but is not included in the criteria for acute kidney failure.<sup>6</sup> Patients with acute kidney failure are also at increased risk of experiencing sepsis and a longer hospital stay.<sup>13</sup> One of the ways to prevent the onset of acute kidney problems in patients after hepatic resection is fluid and electrolyte balance. Adequate and periodic administration of fluids and monitoring of electrolytes plays an important role in preventing the onset of acute kidney failure. Post-resection patients have impaired lactate and phosphate metabolism which causes hyperlactatemia and hypophosphatemia. Due to reduced liver volume and postoperative stress, lactate production increases, and lactate metabolism via gluconeogenesis decreases. This can be used as a guideline for administering low-lactate fluids in post-resection liver management. On the other hand, postoperative ascites may occur especially in patients with underlying cirrhotic disease. In this case, salt restriction and fluid regulation by administering

diuretics can be given.<sup>14</sup>

Liver resection can increase the risk of fluctuations in blood glucose; hence, close monitoring of the patient's glycemic control is necessary. From the above case series based on Table 2 and Figure 5, an increase in blood sugar level  $> 180$  mg/dL was found in 7 out of 11 patients. Hepatocyte ischemic processes and reperfusion increase the risk of both hyperglycemia and hypoglycemia. Furthermore, the duration of occlusion of perfusion to the liver will increase the risk of hyperglycemia during the procedure, thereby increasing the risk of elevated transaminase enzymes (hepatocyte damage). Decreased perfusion to liver tissue will reduce hepatic glucose production so that massive glycogenolysis will occur as compensation. After reperfusion to the liver, glucose will spread to the systemic circulation, resulting in hyperglycemic conditions. Hyperglycemia conditions can increase microcirculation damage and oxidative stress which further damage insulin sensitivity and insulin secretion from the pancreas. However, liver resection can also lead to hypoglycemia, particularly due to a decrease in the capacity of the liver to store glycogen and a decreased gluconeogenesis process.

In patients after liver resection, hypercoagulability may occur. In patients after general, the incidence of hypercoagulability including deep vein thrombosis and pulmonary embolism varies between 15-40% and is associated with a prolonged hospital stay, morbidity, and mortality. This can be prevented by early mobilization, as well as pharmacological treatment such as anticoagulants. In patients after liver resection, the risk of bleeding after the surgery itself results in the limitations and fears of using anticoagulants to prevent hypercoagulable conditions. Patients following liver resection are associated with an increased risk of hypercoagulation. In patients after liver resection, the production of coagulant factors is decreased, but the anticoagulant factors are also decreased by more than 50%. On the other hand, in patients with liver resection, there are increased levels of the von-Willebrand factor, factor VIII, prothrombotic marker sP-selectin, and the thrombin-antithrombin complex, which in turn can create prothrombotic conditions.<sup>14</sup> The patients in this case series all had elevated levels of D-Dimer, ranging from 2,350-11,822 ng/mL. In this case series, patients were given heparin starting 6 hours after resection, which was then adjusted according to serial PT and APTT levels.

If complications and liver failure have occurred after

hepatectomy, it is advisable to maintain the patient's central venous pressure in the range of 8-12 mmHg with a mean arterial pressure (MAP) of 65-90 mmHg, urine output  $\geq 0.5$  mL/kgBW/day, platelet count  $\geq 50,000$ , INR  $\leq 1.5$ , enteral nutrition at least 2,000 kcal/day, and prevention of hepatic encephalopathy.<sup>11</sup> Supplementation of branched-chain amino acids is recommended especially in cirrhotic patients because it may improve the quality of life. Furthermore, renal replacement therapy should be considered if there are signs of acute renal failure leading to hepatorenal syndrome.

## CONCLUSION

Liver resection is one of the main treatment options for patients with liver malignancy with certain criteria. In perioperative monitoring, several important things must be monitored, particularly the decreased hemoglobin levels to monitor perioperative bleeding complications, and liver function monitoring including AST, ALT, bilirubin, and INR to detect the possibility of liver failure. Monitor metabolic parameters, including kidney function and blood glucose. Periodic monitoring of creatinine levels including urine output is important in detecting acute renal impairment and early treatment of these disorders. In addition, monitoring of fluid and electrolyte balance is also important because, in post-liver resection patients, fluid excess or deficiency can increase morbidity and mortality. This monitoring requires multidisciplinary collaboration and holistic treatment to prevent post-resection liver failure and reduce mortality.

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