

## Liver resection profile in Prof. dr. R.D. Kandou General Hospital: 1-year experience



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### ABSTRACT

**Background:** The role of liver surgery is increasing for primary and secondary liver tumors. One of the most feared complications of liver surgery is Post-Hepatectomy Liver Failure (PHLF). The authors would like to present their experience in a year for liver surgery with morbidity and mortality, including PHLF as evaluation parameters.

**Methods:** This is a prospective study from July 2019-2020 in a single-center, in which patients with pre-existing liver pathology were assigned to receive liver resection. Types and duration of liver resection, duration of Pringle maneuver, and blood loss were measured. PHLF was evaluated using the ISGLS classification, and morbidity was evaluated using Clavien-Dindo and FABIB classification. The energy device used varies from the harmonic scalpel, ligature, and Thulium-doped fiber laser (TDFL). Data were processed descriptively with IBM SPSS 25 (SPSS Inc., Chicago, USA). Data are presented in descriptive frequency tables as medians and means.

**Results:** A total of 17 procedures were performed, including minor hepatectomies (58.82 %) and major hepatectomies (41.18%). The mean duration of operation 5.3 hours, the duration of parenchymal transection 91.5 minutes, and the estimated blood loss 1638.2 cc. Vascular occlusion method using Pringle maneuver with mean duration of 31.67 minutes. PHLF incidence found were grade B (5.88 %) and grade C (11.7%), while morbidities by Clavien-Dindo mostly are grade 2 (38.2%) and FABIB classification mostly are Bleeding (45%). The mean postoperative ICU is 3.06 days, and the mortality rate is as high as 23.52%.

**Conclusion:** Liver resection in our center is quite fair judging from the low incidence of PHLF, although the mortality rate is at 23.52%. Due to that, surgical technique and teamwork between units involved need to be improved even further.

**Keywords:** Liver resection, hepatectomy, PHLF.

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### INTRODUCTION

The incidence of cancer or malignancy continues to increase globally. The National Cancer Statistics (NCS) recorded an increase in cancer incidence ranging from 363-517 cases per 100,000 population with liver cancer as one of the etiologies.<sup>1</sup> In 2018, liver cancer ranked the fifth most common cancer with 5.7% of all cancer cases. Liver cancer had a prevalence of 841,080 cases, followed by 781,631 deaths.<sup>2</sup> *American Cancer Society* (ACS) predicts liver cancer prevalence in 2020 by about 42,810 new cases.<sup>3</sup> More than 70% of liver cancer cases occurred in Asia,<sup>4</sup> especially in East Asia and Southeast

Asia. The incidence could reach 17.7 cases per 100,000 population.<sup>5</sup> In Indonesia, liver cancer is the fourth highest cause of cancer (8.9%), with 12.4 per 100,000 population.<sup>6</sup> This number is higher than the world average incidence of 7.6 cases per 100,000 population, and men have four times the risk of women.<sup>4,5</sup> The liver cancer mortality rate can reach 93% and is recorded as the third-highest globally.<sup>7</sup> Despite the significant development of early screening, liver cancer patients' 5-year life expectancy is reported to be only 16% without adequate management.<sup>8</sup> Primary liver cancer is divided into several types, 80% are hepatocellular

carcinoma (HCC), and other forms such as intrahepatic cholangiocarcinoma, angiosarcoma and hepatoblastoma.<sup>9</sup> Thus, the epidemiological picture of primary liver cancer, more or less, reflects the epidemiological description of HCC. Also, liver tumors can be metastases from other primary malignancy with colorectal adenocarcinoma as the most common etiology in men (25%) and breast malignancy in women.<sup>4</sup>

Chronic liver disease is the largest risk factor and is found in 70-90% of patients with HCC.<sup>10</sup> There are variations in the causes of chronic liver disease where chronic hepatitis B infection (HBV) is a

**Table 1. The Brisbane 2000 terminology of liver resection.**

First Order Division		
Anatomical Term	Couninaud segment refer to	Term of surgical resection
Right Hemiliver Or Right Liver	Sg 5-8 (+/-Sg1)	Right Hepatotomy Or Right Hemihepatectomy
Left Hemiliver Or Left Liver	Sg 2-4 (+/-Sg1)	Left Hepatotomy Or Left Hemihepatectomy
Second Order Division		
Anatomical Term	Couninaud segment refer to	Term of surgical resection
Right Anterior Section	Sg 5,8	Right anterior sectionectomy
Right Posterior Section	Sg 6,7	Right posterior sectionectomy
Left Medial Section	Sg 4	Left Medial Sectionectomy / Resection Segment 4 / Segmentectomy 4
Left Lateral Section	Sg 2,3	Left Lateral Sectionectomy / Bisegmentectomy 2,3
Third Order Division		
Anatomical Term	Couninaud segment refer to	Term of surgical resection
Segment 1-9	Any one of Sg 1 to 9	Segmentectomy
2 contiguous segments	Any two of Sg 1 to Sg 9 in continuity	Bisegmentectomy
Other Sectional		
Anatomical Term	Couninaud segment refer to	Term of surgical resection
	Sg 4-8 (+/-Sg1)	Right Trisectotomy / Extended Right Hepatectomy / Extended Right Hemihepatectomy
	Sg 2, 3, 4, 8 (+/-Sg1)	Left Trisectotomy / Extended Left Hepatectomy / Extended Left Hemihepatectomy

risk factor in 50% of all cases and is the predominant cause in Asia's endemic areas (75-90%), except Japan.<sup>11</sup> Apart from chronic viral infection, another significant risk factor is chronic exposure to the hepatic carcinogenic substance Aflatoxin B1 (AFB1) produced by *Aspergillus* species, which induces mutations in segment 7 of the hepatocyte tumor-suppressor gene p53 (R249S) and can be found in grains, nuts and cereals, stored in humid places in tropical countries.<sup>12</sup> The synergy of chronic exposure to HBV and AFB1 increases the relative risk of developing HCC from 3.4-7.3 to 54.1 times, which explains the high prevalence of HCC in Asian countries.<sup>13</sup>

Surveillance data to date have shown a high mortality rate and an increased incidence of HCC, so that comprehensive management is needed. Although non-operative management has developed significantly, surgery is still the main management line and can be curative for treating HCC.<sup>14</sup> Various variables influence the pre and postoperative evaluation of the patient, such as general status, comorbid disease, Milan criteria, Child-Pugh Score

(CPS), resection procedures, and others. Milan criteria parameters consisted of a single lesion diameter < 5cm, diameter < 3cm for a maximum of 3 lesions, absence of vascular and extrahepatic invasion.<sup>15,16</sup> In HCC patients who meet Milan criteria, the 5-year life expectancy after hepatic resection can be > 50%.<sup>17</sup> Child-Pugh Score (CPS) is an assessment criterion to assess the quality of liver function. In the clinical practice of HCC patients, CPS is used to determine the eligibility of patient resection. CPS assesses liver quality through encephalopathy status, degree of ascites, serum bilirubin value, prothrombin time (PT) and albumin levels. The CPS score is then divided into 3 classes, namely, class A (score 5-6), class B (score 7-9) and class C (score 10-15). In practice in HCC patients, class A is generally considered to be suitable for resection.<sup>18</sup>

Resection of the liver in liver cancer patients is different from resection of non-malignancy. Several specific variables such as metastatic probability, vascular control and liver tissue vitalization will influence the postoperative outcome. Metastasis

from other primary malignancy occurs via portal vascularization and can lead to intrahepatic metastases, so structured resection is necessary to avoid metastases. Bleeding is a variable that significantly influences the postoperative outcome, so reasonable vascular control is needed to minimize blood loss. There are various vascular occlusion/clamping methods such as the Pringle Maneuver (portal triad clamping), selective/total clamping, intraglissonian clamping, and total hepatic vascular exclusion (THVE). Apart from the method, vascular occlusion can also be viewed from the duration of exposure to ischemic hepatic parenchyma intermittently or continuously. Intermittent occlusion refers to a changing occlusion pattern (mean about 15-20 minutes) followed by a reperfusion period (generally 5 minutes).<sup>16,17</sup>

Meanwhile, continuous occlusion shows a complete occlusion state without reperfusion during transection. Liver transection techniques are critical to the postoperative outcome and is an emerging part of the realm of liver resection. Some of the widely applied techniques

include crushing techniques, ultrasonic dissection (most commonly with the CUSA Cavitron or Harmonic Scalpel) and sealing devices. The choice of method is determined by the type of resection performed, the tumor's location and size, the value of the preoperative hepatic function, the hemodynamic effects, and the physiological tolerance of future liver remnant (FLR) and the burden of treatment costs. Even with adequate preoperative preparation, complications after hepatic resection with post hepatectomy liver failure (PHLF) being the most feared one, still occur with a mean incidence ranging from 0.7-35% and are the main cause of perioperative mortality.<sup>16-18</sup> There are various indicators used as a parameter to assess the status of post-resection patients, but until now, there is no single indicator to assess the outcome of hepatic resection. There are no national statistical data regarding the epidemiological picture of liver resection related to malignancy until this writing. In this paper, we will describe the demographic aspects, techniques and outputs after hepatic resection in Prof. Dr. Kandou General Hospital, Manado, North Sulawesi.

## METHOD

### Terminology

This paper refers to Brisbane 2000 terminology. Named resections based on the order in which the segments are involved (Table 1).

### Sample

Data collection was carried out prospectively for one year in July 2019 - July 2020 on patients diagnosed with liver tumors at Prof. Dr. R.D. Kandou General Hospital, Manado, North Sulawesi.

### Preoperative Evaluation

The patient's preoperative assessment includes diagnosing tumor type and metastases, comorbid disease, complete hematology panel, PT/APTT, INR, bilirubin, and creatinine panels. The quality of liver function was assessed using the Child's-Pugh Score (CPS). The anesthesia department carries out anesthesia administration and preoperative examinations.

**Table 2. Demographic, clinical data and preoperative liver function panel examination**

Parameter	Mean ± SD	Range
Demographic character		
<b>Gender, n(%)</b>		
Male	11(64.7%)	
Female	6(35.3%)	
Age	56.24±9.7	39-73
<b>Preoperative lab values</b>		
PT (s)	14.17±2.3	9.5 - 19.5
APTT (s)	36.8±6.65	25.2 - 47.3
INR	1.07±0.16	0.87 - 1.29
Total Bilirubin (mg/dL)	1.9±3.4	0.58 - 14.5
Direct Bilirubin (mg/dL)	1.3±2.8	0.2 - 11.75
Serum creatinine (mg/dL)	0.92±0.3	0.5 - 1.4
HBsAg +, n(%)	5(29.4%)	
<b>Child's-Pugh Score</b>		
A, n(%)	14(82.4%)	
B, n(%)	3(17.6%)	
<b>Tumor origin</b>		
Primary, n(%)	10(58.8%)	
Metastasis, n(%)	5(29.4%)	
Others, n(%)	2(11.8%)	

PT = Prothrombin time, APTT = Activated partial thromboplastin time

INR = International normalized ratio, HBsAg = Hepatitis B surface antigen

### Intraoperative Procedures

The intraoperative assessment was carried out based on the total duration of surgery, type, approach and complexity of resection, vascular occlusion technique, clamping duration, technique and duration of parenchymal transaction, and intraoperative amount bleeding (along with total transfusion) up to the first 24 hours postoperatively.

### Postoperative Evaluation

All patients were admitted to the postoperative intensive care unit (ICU) and were assessed for bilirubin, PT / APTT and INR panels on days 1, 3 and 5 postoperatively, while creatinine was assessed for 48 hours postoperatively. The highest peak serum bilirubin was then recorded. PHLF was assessed using PHLF criteria - International Study Group of Liver Surgery (PHLF-ISGLS), and morbidities using Clavien-Dindo and

FABIB classifications. Besides, the duration of care in the ICU and the nursing-ward was also assessed. Postoperative mortality was defined as death in the first 90 days postoperatively without any other cause outside the diagnosis indicated for surgery.

### Statistical assessment

Data were processed descriptively with IBM SPSS 25 (SPSS Inc., Chicago, USA). Data are presented in descriptive frequency tables as medians and means.

## RESULT

### Clinical and Pathological Data

Seventeen patients were included in this study, and informed consent (IC) was approved. The majority of the patients were male (64.7%), with a ratio of 1: 1.83 to women. The median age of our patients was 57 years, with a range of 39-73 years. The pathological data included the CP scoring used as resection reference which

**Table 3. Intraoperative characteristics**

Parameter	n(%)
Duration, ( <i>mean</i> ) hours	5.3±2.2 (2 – 9)
Type of resection	
Major Hepatectomy	7 (41.18%)
Minor Hepatectomy	10(58.8%)
Approach	
Intrafacial	4(23.5%)
Glissonean	13(76.5%)
Parenchymal transection	
Harmonic scalpel	10(58.8%)
TDFL	7(41.2%)
Transection duration, ( <i>mean</i> ) minute	91.5±45 (30 – 180)

**Table 4. Management data and the amount of intraoperative blood loss**

Parameter	Mean
Vascular occlusion, <i>n</i> (%)	
<i>On-demand</i> Pringle	10(58.8%)
<i>Intermittent</i> Pringle	3(17.6%)
Nil	4(23.6%)
Clamping duration (min)	31.67
Total blood loss (cc)	1638.2
Total transfusion (unit)	2

14 patients (82.4%) were included in CPA with all 5 in this class. Evaluation of tumor origin showed the majority of primary liver tumors (58.8%) with 11.8% non-malignant diagnoses, namely, recurrent hepatic cysts suspected of hydatid disease and polycystic liver disease. In the primary liver tumor group, HCC was the main etiology (80%), and cholangiocarcinoma was the group's etiology. Meanwhile, in the metastatic group, all (29.4%) were metastatic colorectal carcinomas (MCRC).

The liver function panel was assessed by PT, APTT, INR, total bilirubin and direct bilirubin. Serum creatinine was assessed for comparison with postoperative creatinine. Hepatitis B virus serologic markers were examined through HBsAg, which gave positive results in 5 (29.4%) patients. The value of direct preoperative bilirubin examination in all patients

increased (the highest value was 11.75 mg / dL), and there were three patients with increased total bilirubin values. In our study, there was only one patient with an increase in INR. Descriptions of demographic parameters and preoperative laboratory panels are listed in [Table 2](#).

#### Operating Characteristics

Of the 17 patients, major hepatectomies (41.18%), minor hepatectomies (58.82%), 1 patient received the hybrid type of surgery (laparoscopic with aspects of open parenchymal resection). Most of the vascular control approaches were the Glissonean pedicle approach (76.5%), intrafascial approach (23.5%). Liver Parenchymal transection used 2 different kinds of energy devices, namely harmonic scalpel (58.8%) and thulium-doped fiber laser (TDFL) device (41.2%). The mean

total surgery duration was  $5.3 \pm 2.2$  hours, and the duration of parenchymal transection was  $91.5 \pm 45$  minutes ([Table 3](#)). Intraoperative blood loss was 1638.2. All vascular occlusion was performed using the Pringle method, on-demand and intermittent, with a mean duration of  $31.67 \pm 22.8$  minutes ([Table 4](#))

#### Postoperative evaluation

Total patients who underwent liver resection were 17 patients with five mortalities in the period <90 days after surgery and one death with an unrelated cause (outside the study period), so the case fatality rate (CFR) of this study was 29.4%. The causes of death consisted of PHLF (11.7%), uncontrolled coagulopathy (5.8%) and systemic inflammatory response syndrome (SIRS) - multiple organ failure (MOF) (5.8%). The mean length of stay in the intensive unit was  $3.06 \pm 4.7$  days. The most prolonged duration of ICU stay was 21 days ([Table 5](#)).

Postoperative morbidities were assessed with Clavien-Dindo (CD) classification and the FABIB score. CD classification, Grade I ( $n = 2$ , 11.7%), Grade II ( $n = 10$ , 58.8%), Grade IVb ( $n = 1$ , 5.8%), Grade V ( $n = 4$ , 23.5%). FABIB Score, Grade A ( $n = 9$ , 52.94%), Grade B ( $n = 2$ , 11.7%), Grade C ( $n = 4$ , 23.5) ([Table 5](#)). While PHLF incidence with PHLF-ISGLS Criteria were, Grade A (82.35%), Grade B (5.8%), Grade C (11.7%) ([Table 6](#)).

The PHLF is generally assessed at the same time as the fifth day of INR. In this study, we reported the INR of 15 patients (the other 2 patients died before the fifth postoperative day) with a median of 1.28 seconds. In all patients, it was found that the postoperative INR value increased significantly with a median of 1.4 seconds and the median fell to within normal limits on the fifth day, namely 1.28 seconds. The highest fifth day's INR value was 1.63 seconds ([Table 7](#)).

Assessment of the bilirubin panel of 15 patients, the trend of the mean total and direct bilirubin values in 13 patients decreased by day 5, but in 2 patients, the total and direct bilirubin values increased during the treatment period. Where in 1 patient, the peak total bilirubin value was 21.57 mg / dL with direct bilirubin 17.69 mg / dL on the 16th postoperative

**Table 5. Evaluation of postoperative complications based on the Clavien-Dindo classification**

Clavien Dindo	Total (n=24)	Complications
None	1(4.1%)	-
Grade I	3(12.5%)	Diuretics, wound infection
Grade II	13(38.2%)	Blood transfusion
Grade IIIb	-	-
Grade IIIb	1(4.1%)	Bleeding
Grade IVa	-	-
Grade IVb	2(8.3%)	Hepatic complication, renal complications, Sepsis, Multiple Organ Failure ( MOF )
Grade V	4(16.6%)	Dead

**Table 6. Evaluation of Post Hepatectomy Liver Failure (PHLF) by ISGLS criteria**

PHLF-ISGLS	Total (n=17)	Complications
Grade A	14(82.35%)	Adequate coagulation, No symptoms of uremia, saturation >90%
Grade B	1(5.8%)	Ascites
Grade C	2(11.7%)	Encephalopathy, Renal failure

**Table 7. Evaluation of FABIB scores**

FABIB	Total (n=20)	Complications
None	5(25%)	-
Grade A	9(45%)	Ascites, Bleeding, bile leakage, infection, bleeding
Grade B	2(10%)	Infection
Grade C	4(20%)	Failure, Ascites, Infection

**Table 8. Postoperative liver function panel values**

	Postoperative day		
	Day 1	Day 3 Mean	Day 5
Total Bilirubin	2.26 (1.1)	1.7 (1.17)	1.6±2.1 (1.6)
Direct Bilirubin	1.5 (0.58)	1.2 (0.535)	1.1 (1.14)
PT	23.2 (17.8)	17.8 (17.2)	14.98 (16.15)
APTT	45.8 (36.3)	38.7 (39.8)	35.5 (35)
INR	1.9 (1.4)	1.48 (1.34)	1.2 (1.28)

day. Meanwhile, for the APTT value, the median APTT on the first day after surgery was higher than preoperative and peaked on the third day of assessment with a median of 39.8. Renal function was assessed by creatinine, and in all patients, pre and postoperative creatinine values were within normal limits (preoperative

median 0.9, postoperative median 1.0). Table 5 shows the hepatic function value data. Postoperative histopathological examination recorded eight patients with HCC, four patients with MCRC, one cholangiocarcinoma, three non-malignant etiologies

## DISCUSSION

Resection of the liver in liver cancer patients is different from resection of non-malignancy. Several specific variables such as metastatic probability, vascular control and liver tissue vitalization will influence the postoperative outcome

Types of resection were minor (76.5%), major (23.5%). Most of the approaches were done Glissonean (n = 13, 76.5%) and non-anatomical (n = 4, 23.5%). Parenchymal transection used two modes: harmonic scalpel (58.8%) and thulium laser device (41.2%). The mean total operation duration was 5.3 hours, and the duration of parenchymal transection was 91.5 minutes. The number of bleeding listed was the total amount of intraoperative bleeding and 24 hours postoperatively with a mean of 1638.2. Three patients received fresh frozen plasma (FFP) transfusions. All vascular occlusion was performed using the Pringle method, on-demand and intermittent, with a mean duration of 31.67 minutes.

Various variables affect the patient's pre and postoperative evaluation, such as general status, comorbid disease, Milan criteria, Child-Pugh Score (CPS), resection procedures, and others. Milan criteria parameters consisted of a single lesion diameter <5cm, diameter <3cm for a maximum of 3 lesions, absence of vascular and extrahepatic invasion.<sup>15,16</sup>

Postoperative complications were assessed using three tools: the Clavien-Dindo score (C-D), PHLF-ISGLS and FABIB scores. The C-D score was assessed on the fifth postoperative day, and as many (38.2%) patients entered grade II and were entirely due to blood product transfusions because liver resection is a relatively new procedure at our site, so learning is still needed. Based on the PHLF-ISGLS criteria (76.47%), the patients were classified as grade A, only deterioration in liver function without clinical symptoms, because most of the vascular control approaches were Glissonean pedicle approach. The FABIB score showed (45%) complications were included in grade A with the most common complications in ascites, bleeding, bile leakage, infection, bleeding, and infection after the clean-contaminated surgery. The case fatality rate (CFR) of this study was 29.4%. The

causes of death consisted of PHLF (11.7%), uncontrolled coagulopathy (5.8%) and systemic inflammatory response syndrome (SIRS) - multiple organ failure (MOF) (5.8%). The mean length of stay in the intensive unit was  $3.06 \pm 4.7$  days. The most prolonged duration of intensive unit care was 21 days.

## CONCLUSION

Liver resection in our center is quite fair judging from the low incidence of PHLF, although the mortality rate is at 23.52%. Due to that, surgical technique and teamwork between units involved need to be improved even further.

## DISCLOSURE

### Conflict of Interest

The authors declare no conflicts of interest that pertain to this work.

### Funding

This study was self-funded by authors.

### Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to account for all aspects of the work.

### Ethical Statement

This study has approved by the Ethic Commission of Universitas Sam Ratulangi.

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