Original Article

Original Article

Predictors for 30-day mortality in hepatocellular carcinoma patients undergoing liver resection

Erik Prabowo[1,2,3,4], Neni Susilaningsih[5,6*], Catharina Suharti[7,8], Hery D. Purnomo[9,10], Ignatius Riwanto[2,3], Ahmad F. Fuadi[2,3], Ardiyana Ar[11], Beatrice LA. Bulandari[11], Kevin C. Tjandra[11], Danendra RK. Respati[11] and Derren DCH. Rampengan[4]

[1]Doctoral Study Program of Medical and Health Science, Universitas Diponegoro, Semarang, Indonesia; [2]Division of Digestive Surgery, Department of Surgery, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia; [3]Division of Digestive Surgery, Department of Surgery, Kariadi Hospital, Semarang, Indonesia; [4]Faculty of Medicine, Universitas Sam Ratulangi, Manado, Indonesia; [5]Department of Biomedicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia; [6]Department of Histology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia; [7]Division of Oncology Hematology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia; [8]Division of Oncology Hematology, Department of Internal Medicine, Kariadi Hospital, Semarang, Indonesia; [9]Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia; [10]Division of Gastroenterohepatology, Department of Internal Medicine, Kariadi Hospital, Semarang, Indonesia; [11]Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

*Corresponding author: nsusilaningsih@gmail.com

Abstract

Hepatocellular carcinoma (HCC) ranks among the most prevalent and fatal liver cancers globally. Liver surgery, particularly resection, offers the potential for cure but poses challenges, especially in Indonesia, where patients often present in advanced stages. This study aimed to determine the intraoperative and perioperative factors associated with 30-day mortality of HCC patients undergoing liver resection at a tertiary referral hospital. The study included HCC patients undergoing liver resection at Karadi General Hospital, Semarang, Indonesia, between January 2018 and September 2023. Demographic data, intraoperative, perioperative, and postoperative factors were collected, with the primary outcome being 30-day mortality. Factors influencing 30-day survival were assessed using a log-rank test and the survival analysis employed Kaplan-Meier curves. Among 58 HCC patients who had liver resection, 62.1% were males, with a mean age was 57.27±9.56 years. Preoperative comorbidities, notably hepatitis B, affected 34.4% of patients. Child-Pugh Score categorized 91.4% as class A. The study found a 30-day mortality rate of 10.3% with no subsequent increase in incidence. The failure-to-rescue rate (FTR) of this study was found 46%. Factors associated with 30-day mortality were Child-Pugh classification ($p<0.001$), intraoperative bleeding ($p=0.001$), creatinine levels ($p=0.005$), Clavien-Dindo classification ($p<0.001$), and posthepatectomy liver failure (PHLF) ($p<0.001$). This study suggests that preoperative (Child-Pugh classification), intraoperative (blood loss volume), and postoperative factors (Creatinine level, Clavien-Dindo classification, and PHLF) could predict the mortality rate of HCC patients undergoing liver resection.

Keywords: Liver resection, predictive, mortality, morbidity, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, ranking as the sixth most diagnosed cancer globally and the fourth leading cause of cancer-related death in 2018 [1]. Approximately 72% of HCC cases and associated deaths were recorded in Asia, including

Received: June 18, 2024 - Accepted: October 10, 2024 - Published online: October 11, 2024

Indonesia [2]. Liver resection, along with ablation and transplantation, are the curative options for HCC [3]. Liver resection offers good overall survival, with 5-year rates ranging from 38% to 61%, depending on the stage and the presence of metastasis [4,5]. Due to limited donor availability and the ineffectiveness of ablation for large lesions, liver resection is the most common curative approach. However, postoperative mortality remains high, with post-hepatectomy liver failure (PHLF) being the leading cause of death [6,7]. A recent study reported that mortality rates following liver resection for HCC can be reduced to 4% with the reduction of risk factors, operative techniques, and perioperative management [8].

In Indonesia, a study showed that the one-year HCC survival rate remains low, at 29.4%, with a median survival duration of 138 days [2]. This prompts questions about whether liver resection is the appropriate choice for HCC patients. Individuals with massive HCC, low serum α-fetoprotein (AFP), a low incidence of cirrhosis, and high mortality are considered to be in an advanced stage; thus, they are poor candidates for curative resection [9]. However, recent standardized criteria for liver resection surgery are limited to single nodules and adequate liver function or Child-Pugh class A cirrhosis as key considerations [10]. Therefore, appropriate patient selection for HCC remains elusive, requiring the identification of perioperative factors that predict poor prognosis post-liver resection to avoid unnecessary challenges for patients [8].

Analyzing postoperative factors is crucial for predicting complications and mortality after liver resection [11]. Effective management requires an understanding of liver metabolism, including fluid and electrolyte balance, nutrition, and coagulopathy [12]. Furthermore, pain management and infection risk reduction are significant contributors to postoperative morbidity and mortality in liver resection [13]. Proper management of perioperative factors in HCC patients after liver resection is essential to improve prognosis and achieve optimal outcomes [14].

A study indicated that older age, poor liver function (Child-Pugh B/C), and major resections were significant predictors of postoperative mortality [15]. Additionally, the need for blood transfusion and prolonged operative time were also associated with higher morbidity [15]. The aim of this study was to investigate the risk factors in the preoperative, intraoperative, and postoperative phases in HCC patients undergoing liver resection to predict mortality within 30-day and 90-day periods post-liver resection.

Methods

Study design and setting

A retrospective cohort study was conducted at Kariadi Hospital, Semarang, Central Java, Indonesia, from January 2018 to September 2023, involving HCC patients who underwent liver resection. All HCC patients who met the criteria were evaluated, including the patient demographics, preoperative details, intraoperative performance, and 30-day postoperative mortality, collected from the hospital's electronic medical records, combined with in-person visits and telephone interviews conducted by trained research coordinators and clinical nurse specialists. The follow-up also collected information on patient well-being and complications, which were categorized using the Clavien-Dindo (CD) classification for reporting surgical complications.

Sampling strategy and patient criteria

All HCC patients who underwent liver resection during the study period were considered eligible. Total sampling was employed based on inclusion and exclusion criteria. Inclusion criteria were: (1) patients who underwent complete liver resection at Kariadi Hospital, Semarang, Central Java, Indonesia, between January 2018 and September 2023; and (2) patients with a postoperative histopathological diagnosis of HCC. Patients who underwent partial liver resection, including R1 (microscopically incomplete resection) or R2 (macroscopically incomplete resection) and those patients lacking detailed preoperative records and consistent postoperative follow-up.

Data collection

Clinical indication for liver resection was based on computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or elevated serum α-fetoprotein (AFP) levels. CT scan and MRI findings indicated the need for liver resection in patients with resectable HCC lesions exhibiting typical imaging features, such as arterial phase hyperenhancement followed by washout in the portal venous or delayed phases, without major blood vessel involvement or extrahepatic spread, and with adequate future liver remnant volume. The serum AFP levels >20 ng/mL, particularly >400 ng/mL, further corroborated the diagnosis, provided that patients had sufficient liver function and no significant comorbidities contraindicating surgery.

Liver resection was performed by experienced digestive surgeons following a standardized protocol. While the standardized protocol was designed to reduce differences in surgical techniques, variations in individual surgeon experience and technique could still influence intraoperative risks and, consequently, patient outcomes. This variability was accounted for in the study to ensure a comprehensive assessment of risk factors affecting morbidity and mortality in HCC patients undergoing liver resection.

Preoperative, postoperative, and follow-up evaluations were conducted for each patient. Each patient was followed for up to 90 days postoperatively. Follow-up methods employed in this study included a combination of in-person visits at one week, one month, and three months postoperatively conducted by the primary surgical team for physical examinations and clinical assessments and telephone interviews at week 2 and month 2 postoperatively performed by trained research coordinators or clinical nurse specialists. The follow-ups collected information on patient well-being and complications. Continuous monitoring through electronic health records was reviewed by research coordinators and data analysts to track hospital readmissions, emergency visits, and any additional tests or procedures, ensuring comprehensive monitoring of patient outcomes.

Study variables and measurements

Patients' demographics, including age, sex, and body mass index (BMI), were documented. Age was classified as adult (18–59 years) and elderly (60 years and older). BMI was calculated based on body weight and body height of patients, categorized as underweight (range: <18.5 kg/m^2), normal (range: 18.5–24.9 kg/m^2), overweight (range: 25–29.9 kg/m^2), and obese (range: ≥30 kg/m^2). Patient mortality at 30 and 90 days postoperatively was documented using continuous review of electronic health records by research coordinators and data analysts, scheduled telephone interviews at two weeks and two months, in-person follow-up visits at week, one month, and three months conducted by the primary surgical team, and direct contact with family members or caregivers to ensure comprehensive data collection.

Preoperative evaluation

Preoperative evaluation included the type of tumor, the presence of metastasis, comorbidities, history of prior liver or abdominal surgery, and liver function quality. Tumor type was diagnosed using imaging studies such as CT scans and MRIs, along with histopathological examination of biopsy samples, following the Barcelona Clinic Liver Cancer (BCLC) and American Joint Committee on Cancer (AJCC) TNM staging systems, interpreted by a multidisciplinary team including radiologist, pathologist, and hepatologist [16,17].

Metastasis, evaluated by an oncologist, radiologist, and surgeon, was assessed through imaging studies and classified using the AJCC TNM system [16]. Comorbidities documented in the present study included hepatitis B, hepatitis C, coronary heart disease, diabetes mellitus, bladder carcinoma, hypertension, azotemia, and malnutrition. In liver resection, coronary artery disease (CAD) and azotemia are directly related to outcomes due to their impact on cardiovascular and renal function, respectively, increasing the risk of complications, while bladder carcinoma has a more indirect effect, potentially complicating postoperative management and overall [18-20].

Liver function quality was assessed using the Child-Pugh score. This scoring system, primarily used to assess mortality risk and liver function severity in cirrhosis patients, was utilized to evaluate the liver's functional reserve and predict postoperative outcomes in liver resection patients. The Child-Pugh score evaluates liver function and prognosis by assessing total bilirubin, serum albumin, prothrombin time, ascites, and encephalopathy, with each criterion scored from 1 to 3 points, resulting in a total score ranging from 5 to 15 [21]. It was classified as

Class A (mild disease, better prognosis), Class B (moderate disease, intermediate prognosis), or Class C (severe disease, poor prognosis).

Intraoperative evaluation

The intraoperative evaluation included surgical duration, resection type, surgical complexity, vascular occlusion method (Pringle maneuver type), and intraoperative bleeding volume. The time for surgical duration referred to the total time from the initial skin incision to the final skin suturing, encompassing all stages of the operation, including tumor resection, vascular control, and hemostasis, and was used to evaluate surgical complexity and its potential impact on patient outcomes.

Resection type was categorized as laparoscopy or laparotomy, with surgical complexity classified as minor or major, categorized based on the International Hepato-Pancreato Biliary Association [22]. Minor resection when the segmental or wedge resection removed ≤2 adjacent Couinaud segments, while major liver resection was defined as the resection of 3 liver segments or more. The vascular occlusion method employed the Pringle maneuver with a pattern of 15 minutes on and 5 minutes off, which could be repeated multiple times. Parenchymal transection in this study was performed using an ultrasonic dissector and advanced bipolar. Intraoperative bleeding was classified as moderate (500 to 1,000 mL) or severe (exceeding 1,000 mL).

Postoperative evaluation

Patients were admitted to the ICU postoperatively, and some parameters were measured, including bilirubin, creatinine, international normalized ratio (INR), lactate, Clavien-Dindo score, PHLF, and adhesions to neighboring organs on day 5. Clavien-Dindo score or classification is a standardized system used to assess and grade the severity of surgical complications (ranging from Grade I for minor complications to Grade V for death) [23]. The INR normal ranges from 0.8–1.2, with elevated levels indicating coagulation disorder.

Postoperative ICU length of stay, failure to rescue (FTR), and PHLF were also assessed for each patient. The length of stay was documented and presented as continuous data. FTR was defined as mortality following a major surgical complication, calculated using Clavien-Dindo score within 30 days postoperatively to measure the effectiveness of managing severe complications, evaluated by the surgical team using clinical records and follow-up data. PHLF was evaluated using PHLF criteria from the International Study Group of Liver Surgery (PHLF-ISGLS), categorized into Grade A (mild dysfunction without significant symptoms), Grade B (moderate dysfunction with manageable symptoms), and Grade C (severe dysfunction with significant clinical consequences), assessed by the surgical team through clinical observations and laboratory tests [24].

Mortality assessment

Patient survival time was calculated from liver resection to discharge from hospital, 30 days post-surgery, using Kaplan-Meier analysis. The analysis produced a survival-mortality curve and showed the probability in 30 days after the liver resection.

Statistical analysis

Continuous data were presented as mean and standard deviation, while categorical data were presented as percentages. A test for normality, the Shapiro-Wilk test, was performed to determine the data distribution. Factors influencing 30-day survival were assessed using the log-rank (Mantel-Cox) test and the survival analysis employed Kaplan-Meier curves. SPSS version 25.0 software (IBM SPSS, Chicago, Illinois, USA) was used for data analysis, with $p<0.05$ was considered statistical significance.

Results

Characteristics of patients pre-, intra-, and post-surgery

A total of 208 HCC patients underwent liver resection during the study period, but only 58 patients were involved based on inclusion and exclusion criteria. The characteristics of patients

Prabowo et al. Narra J 2024; 4 (3): e1001 - http://doi.org/10.52225/narra.v4i3.1001

are presented in **Table 1**. Males consisted of 62.1% of the samples with a mean age of 57.2 years. Of these, 33 (56.9%) were adults and 25 (43.1%) were classified as elderly. Regarding comorbidity, 75.8% of patients had at least one disease, with 25 (43.1%) having multiple conditions. Hepatitis B infection, detected by HBsAg, was the most common comorbidity, present in 20 (34.4%) patients. Liver function was assessed using the Child's-Pugh score, with category A observed in 53 (91.4%) patients and category B in 5 (8.6%) patients (**Table 1**).

Liver resection lasted on average of 284±105 minutes, ranging from 120 to 600 minutes (**Table 1**). Laparotomy was performed in 49 (84.5%) cases and laparoscopic procedures in nine (15.5%) cases. Among all patients, 38 (65.5%) had major complexity involving three or more resected segments, occasionally requiring the removal of neighboring organs.

During postoperative evaluation, the mean duration of ICU stay was 3.33±1.91 days (**Table 1**). Elevated bilirubin levels (>2 mg/dL) were found in 45 patients (15.5%), peaking at 11.00 mg/dL. Additionally, 20 patients (34.6%) had elevated INR (>1.50), and five patients (8.6%) showed increased creatinine levels. Adhesions to neighboring organs, primarily the diaphragm, stomach, and intestines, were observed in 11 (18.9%) patients, resulting in the resection of affected organs (**Table 1**).

Table 1. Demographic data as well as preoperative, intraoperative and postoperative evaluations of hepatocellular carcinoma (HCC) patients undergoing liver resection (n=58)

Data	Variables	Frequency (%)
Demographic data	Age (years), mean±SD	57.27±9.56
	Adult	33 (56.9)
	Elderly	25 (43.1)
	Sex	
	Male	36 (62.1)
	Female	22 (37.9)
	Body mass index	
	Underweight	0 (0.0)
	Normal	38 (65.5)
	Overweight	2 (3.4)
	Obese	18 (31.0)
Preoperative evaluation	Comorbidity	
	None	12 (20.6)
	Hepatitis B	20 (34.4)
	Coronary artery disease	1 (1.7)
	Diabetes mellitus	1 (1.7)
	Hepatitis C	1 (1.7)
	Bladder carcinoma	1 (1.7)
	Hypertension	4 (6.9)
	Azotemia	1 (1.7)
	Severe malnutrition	1 (1.7)
	Number of comorbidities	
	≤1	44 (75.8)
	>1	14 (24.1)
	Prior history of liver or abdominal surgery	
	Abdominal surgery	3 (5.1)
	Liver resection	2 (3.4)
	None	53 (91.3)
	Major	38 (65.5)
	Child-Pugh classification	
	A	53 (91.4)
	B	5 (8.6)
Intraoperative evaluation	Surgical duration (minutes), mean±SD	284.0±105.5
	Resection type	
	Laparoscopy	9 (15.5)
	Laparotomy	49 (84.5)
	Surgical complexity	
	Minor	20 (34.5)
	Major	38 (65.5)
	Pringle maneuver	
	Yes	22 (37.9)
	No	36 (62.1)
	Vascular occlusion method	
	Clamping duration (minute), mean±SD	24.5±8.2

Data	Variables	Frequency (%)
	Parenchymal transaction duration	46.3±12.5
	Intraoperative bleeding (mL), mean±SD	
	Moderate	47 (79.3)
	Severe	12 (20.6)
Postoperative evaluation	Postoperative ICU length of stay (days), mean±SD	3.3±1.9
	Bilirubin level (mg/dL)	
	Normal	4 (8.2)
	High	45 (91.8)
	International normalized ratio (INR)	
	Normal	23 (53.5)
	Abnormal	20 (46.5)
	Creatinine level (mg/dL)	
	Normal	37 (88.1)
	Abnormal	5 (11.9)
	Lactate level (mmol/L)	
	Normal	6 (11.8)
	Hyperlactatemia	20 (39.2)
	Lactic acidosis	25 (49.0)
	Clavien-Dindo score	
	0–2	43 (76.8)
	3–5	13 (23.2)
	Posthepatectomy liver failure (PHLF)	
	Grade A	16 (69.6)
	Grade B	5 (21.7)
	Grade C	2 (8.7)
	Adhesions to neighboring organ	
	Resection of affected organ	11 (18.9)

Factors associated with mortality

The overall survival analysis is presented in **Table 2**. A total of six patients (10.3%) deceased within 30 days postoperatively, with no subsequent increase in incidence observed up to 90 days postoperatively (i.e., no change between 30 and 90-day mortality). The analysis indicated that five factors were associated with mortality: Child-Pugh classification (p<0.001), intraoperative bleeding (p=0.001), creatinine level (p=0.005), Clavien-Dindo classification (p<0.001), and PHLF classification (p<0.001) (**Table 2**).

Table 2. Risk factors contributing to 30-day mortality and failure-to-rescue rate (FTR) of hepatocellular carcinoma (HCC) patients undergoing liver resection (n=58)

Variables	Death	Survive	p-value §	FTR
	n (%)	n (%)		n (%)
Age				
Adult	2 (33.3)	31 (59.6)	0.227	2 (33.3)
Elderly	4 (66.7)	21 (40.4)		4 (66.7)
Sex				
Male	3 (50.0)	33 (63.4)	0.496	3 (50.0)
Female	3 (50.0)	19 (36.6)		3 (50.0)
Body mass index				
Underweight	0 (0)	0 (0)		
Normal	6 (100)	52 (100)	0.081	6 (100)
Overweight	0 (0)	0 (0)		
Obese	0 (0)	0 (0)		
Preoperative evaluation				
Comorbidity				
None	1 (16.6)	41 (78.8)	0.794	1 (16.6)
Hepatitis B	3 (50.0)	11 (21.2)	0.900	3 (50.0)
Coronary artery disease	0 (0)	0 (0)	0.636	
Diabetes mellitus	1 (16.6)	0 (0)	0.155	1 (16.6)
Hepatitis C	0 (0)	0 (0)	0.740	
Bladder carcinoma	0 (0)	0 (0)	0.740	
Hypertension	1 (16.6)	0 (0)	0.578	1 (16.6)
Azotemia	0 (0)	0 (0)	0.558	
Severe malnutrition	0 (0)	0 (0)	0.740	
Number of comorbidities				
≤1	1 (16.6)	6 (11.5)	0.685	1 (16.6)
>1	5 (83.4)	46 (88.5)		5 (83.4)

Variables	Death	Survive	*p*-value §	FTR
	n (%)	n (%)		n (%)
Child-Pugh classification			<0.001**	
A	2 (33.3)	51 (98.0)		2 (33.3)
B	4 (66.7)	1 (2.0)		4 (66.7)
Intraoperative evaluation				
Resection type			0.909	
Laparoscopy	1 (16.6)	8 (15.3)		1 (16.6)
Laparotomy	5 (83.4)	44 (84.7)		5 (83.4)
Surgical complexity			0.329	
Minor	1 (16.6)	19 (36.5)		1 (16.6)
Major	5 (83.4)	33 (63.5)		5 (83.4)
Pringle maneuver			0.549	
Yes	3 (50.0)	19 (36.5)		3 (50.0)
No	3 (50.0)	33 (63.5)		3 (50.0)
Intraoperative bleeding			0.001*	
Moderate	2 (33.3)	44 (84.6)		2 (33.3)
Severe	4 (66.7)	7 (13.4)		4 (66.7)
Postoperative evaluation				
Bilirubin			0.672	
Normal	3 (50.0)	10 (19.2)		3 (50.0)
High	3 (50.0)	42 (80.8)		3 (50.0)
International normalized ratio (INR)			0.284	
Normal	5 (83.4)	33 (63.5)		5 (83.4)
Abnormal	1 (16.6)	19 (36.5)		1 (16.6)
Creatinine level			0.005*	
Normal	4 (66.7)	49 (94.2)		4 (66.7)
Abnormal	2 (33.3)	3 (5.8)		2 (33.3)
Lactate			0.139	
Normal	1 (16.6)	12 (23.0)		1 (16.6)
Hyperlactatemia	1 (16.6)	19 (36.5)		1 (16.6)
Lactic acidosis	4 (66.7)	21 (40.5)		4 (66.7)
Clavien-Dindo classification			<0.001**	
Clavien-Dindo 0–2	0 (0.0)	45 (86.5)		0 (0.0)
Clavien-Dindo 3–5	6 (100)	7 (13.5)		6 (100)
Posthepatectomy liver failure (PHLF)			<0.001**	
Grade A	2 (33.3)	39 (75.0)		2 (33.3)
Grade B	2 (33.3)	13 (25.0)		2 (33.3)
Grade C	2 (33.3)	0 (0.0)		2 (33.3)

§ Analyze with log-rank (Mantel-Cox) test
* Statistically significant at p=0.05
** Statistically significant at p=0.001

These findings reflect a clear association between preoperative, intraoperative, and postoperative factors, including liver and kidney function, with overall survival outcome underscoring the strong influence of these factors on mortality rate. The study found that the FTR rate was 46%, calculated from six deaths among 13 patients graded Clavien-Dindo classification 3a or higher.

Survival analysis

Kaplan-Meier survival analysis was carried out to assess significant differences related to each factor that contributed to mortality (**Figure 1**). The data also indicated that patients in the Child-Pugh class A group had a significantly higher 30-day survival rate compared to those in the Child-Pugh class B group. Patients with moderate bleeding have a consistently higher 30-day survival probability compared to patients with massive bleeding. Normal creatinine level was associated with better outcomes than abnormal levels. Patients with Clavien-Dindo score 0–2 had higher 30-day survival rate than patients with Clavien-Dindo score more than 3 and those with PHLF grade C had significantly lower 30-day survival rate compared to those in PHLF grade A and grade B (**Figure 1**).

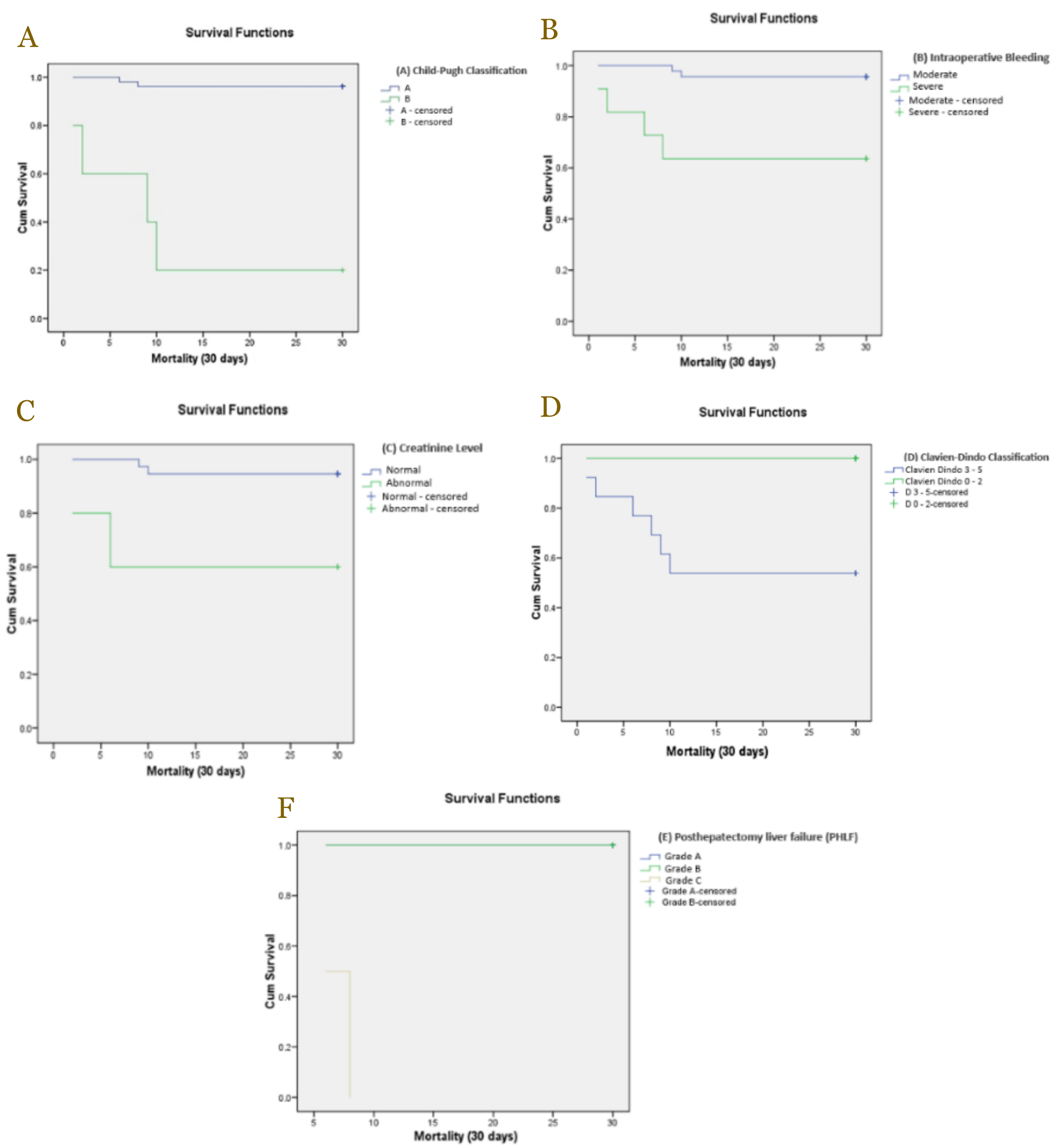

Figure 1. The 30-day mortality rate of hepatocellular carcinoma (HCC) patients following liver resection based on Child-Pugh classification (A), intraoperative bleeding (B), creatinine level (C), Clavien-Dindo classification (D), and posthepatectomy liver failure (PHLF) (E).

Discussion

The present study found 30-day and 90-day mortality rate of 10.3% among HCC patients undergoing liver resection. As a high-volume center in Indonesia, performing over 25 liver resections annually, these mortality rates are higher compared to those reported in Saudi Arabia (5.2%) [25] and the United States (2.6%) [26]. This reflects potential quality gaps between centers in developed and developing countries. However, the 30-day mortality rate of 10.3% in the present study compares favorably with other tertiary referral hospitals in Indonesia, including Cipto Mangunkusumo Hospital, Jakarta (8.8% in-hospital, 11.5% at 30 days, and 24.1% at 90 days) and R.D. Kandau Hospital, Manado (23.52% at 90 days) [27,28].

Significant factors associated with 30-day mortality in the present study included Child-Pugh classification, intraoperative bleeding, creatinine levels, Clavien-Dindo classification, and PHLF. Intraoperative bleeding was the sole intraoperative variable linked to mortality, while the Child-Pugh classification was the only preoperative factor associated with mortality. However, mortality rates were linked to at least three postoperative variables: creatinine levels, Clavien-

Dindo classification, and PHLF. Improving survival for postoperative HCC patients remains a significant challenge due to the high recurrence rates [29]. Some factors have been explored on survival previously, such as patient characteristics (age, gender, hepatitis status, liver function, AFP levels), tumor factors (size, number, vascular invasion, and differentiation) [30], surgical factors such as type of resection, approach, extent, margins, bleeding, and transfusion [31], as well as microvascular invasion [32].

Many studies have reported notable postoperative mortality rates, highlighting the severity of complications following liver resection [8,28,33]. A study reported a 30-day postoperative mortality rate of 5% [8], and another study indicated postoperative mortality rates of 5.1% and 7.1% at 30 and 90 days, respectively [33]. During follow-up, 59% of patients experienced recurrence, with 15.5% requiring re-excision [33]. Immediate postoperative bleeding and liver failure are frequent and severe complications of liver resection [34]. Furthermore, common causes of death following liver resection included PHLF (11.7%), uncontrolled coagulopathy (5.8%), and systemic inflammatory response syndrome (SIRS), leading to multiple organ failure (MOF) (5.8%) [28].

The mortality rate in the present study was significantly associated with FTR, accounting for 46% of patients, based on six deaths among 13 patients graded as Clavien-Dindo classification 3a or higher. Our analysis indicated that the Clavien-Dindo score was also one of the variables that was significantly associated with 30-day mortality. This rate exceeds the global FTR rate in liver resection reported by Elfrink *et al.* (19.1%) [35] and Raptis *et al.* (10%) [36]. Factors contributing to FTR include older age, histopathological cirrhosis, liver resection for bile duct cancer, major liver resection, and the American Society of Anesthesiologists (ASA) 3. The ASA 3 classification refers to patients with severe systemic disease that limits activity but is not incapacitating [36]. Postoperative liver failure, cardiac complications, and thromboembolism are also associated with FTR [36]. The results of the current study underscore the importance of proactively managing complex complications. This approach could reduce the number of patients categorized as Clavien-Dindo Grade 3A or higher and decrease the FTR rate. Consequently, the risk of infectious complications, such as intra-abdominal and surgical site infections, may also be lowered.

To reduce mortality post-liver resection, it is suggested to have aggressive management of postoperative complications and better patient selection [35]. Preoperative assessments such as liver volumetrics, hepatobiliary scintigraphy, and screening for cardiac and thromboembolic complications are recommended [36]. Cardiopulmonary pre-rehabilitation and liver function tests may enhance postoperative care for high-risk patients [23]. Referral of high-risk cases to specialized centers is also advised for comprehensive management of complications [36].

Intraoperative bleeding emerged as a critical factor affecting liver resection outcomes in the present study. Patients experiencing moderate bleeding (100–500 mL) had higher survival rates (80.7%) compared to those with blood loss exceeding 500 mL. Morbidity, hospital stay, and mortality rates significantly increased in patients with blood loss greater than 500 mL [33]. The impact of blood loss and transfusion on outcomes is complex, suggesting potentially challenging resections or underlying cirrhosis with portal hypertension [37]. A study found that blood loss independently correlates with PHLF and mortality, as PHLF significantly increases the risk of 90-day mortality and presents challenges for long-term survival [35].

Although PHLF Grade A is associated with more postoperative complications compared to non-PHLF cases, it does not independently predict 90-day mortality or long-term survival [38]. The impact of PHLF Grade B/C on long-term survival is not observed in patients surviving beyond 90 days post-operation [39]. However, a study reported that PHLF Grades B and C are associated with significant mortality, whereas PHLF Grade A showed no meaningful difference compared to non-PHLF cases [40].

Child-Pugh classification is a reliable predictor of postoperative outcomes in HCC patients with lower Child-Pugh classification correlates with better overall survival [40]. A study underscored that preserving liver function, as assessed by Child-Pugh classification, predicts patient prognosis post-liver resection [41]. Strict preoperative selection criteria, such as limiting resection to fewer than two segments and using a laparoscopic approach for Child-Pugh class A patients, can significantly reduce mortality rates [42].

Postoperative elevated creatinine levels may indicate acute kidney injury (AKI) [43]. A study showed that AKI, characterized by increased serum creatinine, correlates with prolonged hospitalization (p=0.01) and higher 30-day mortality (p<0.01) [43]. Moreover, AKI post-liver resection strongly predicts 90-day mortality [43]. Identifying high-risk patients early post-surgery is crucial, warranting nephrologist consultation and optimizing biomarker efficiency to diagnose AKI promptly [44]. Adequate volume management using diuretics or vasoactive drugs should also be considered to mitigate AKI risks [44].

Aggressively managing perioperative variables is crucial in liver resection surgery for hepatocellular carcinoma [3]. Monitoring comorbidities, preoperative and postoperative liver function tests, and ensuring blood transfusion availability are essential steps [45]. The present study findings suggested considering laparoscopy over open laparotomy, though surgical decisions should be tailored to individual patient conditions based on perioperative variables [46]. Developing clinical practice guidelines for selecting surgical techniques based on these variables could aid surgeons in comprehensive patient management and potentially reduce FTR and mortality rates, particularly in developing countries such as Indonesia [47].

This present study has some limitations that need to be discussed. First, the single-canter design limits the generalizability of its findings, as outcomes and practices may vary across different institutions. The sample size of 58 patients, while providing valuable insights, may not be sufficiently large to detect subtle associations between perioperative factors and FTR. Additionally, the lack of significant independent variables associated with FTR might be attributed to the study's design or sample size rather than the absence of such relationships. The study also did not include a control group or compare outcomes with other centers, potentially missing broader context or variations in perioperative management. To address these limitations, larger, multicentre studies across Indonesia are needed to provide more robust evidence on the impact of perioperative factors on FTR and to enhance the generalizability of the findings.

Conclusion

The 30-day mortality rate was 10.3% among HCC patients undergoing liver resection. Factors influencing FTR in resectable HCC include intraoperative bleeding, Child-Pugh classification, creatinine levels, and PHLF. Addressing these factors may reduce FTR and enhance perioperative preparation for liver resection in HCC patients.

Ethics approval

The protocol of the present study was reviewed and approved by the Ethical Committee of Health Research, Kariadi Hospital, Semarang, Central Java, Indonesia (Approval number: 1689/EC/KEPK-RSDK/2024), and adhered to the Declaration of Helsinki.

Acknowledgments

The authors declare no acknowledgments of this study.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

Prabowo E, Susilaningsih N, Suharti C, *et al*. Predictors for 30-day mortality in hepatocellular carcinoma patients undergoing liver resection. Narra J 2024; 4 (3): e1001 - http://doi.org/10.52225/narra.v4i3.1001.

References

1. Sayiner M, Golabi P, Younossi ZM. Disease burden of hepatocellular carcinoma: A global perspective. Dig Dis Sci 2019;64(4):910-917.
2. Irsan Hasan. Survival in patients with hepatocellular carcinoma fungsi hati dan jenis terapi merupakan prediktor kesintasan pasien karsinoma sel hati. J Penyakit Dalam Indones 2020;7(3):149-153.
3. Vibert E, Schwartz M, Olthoff KM. Advances in resection and transplantation for hepatocellular carcinoma. J Hepatol 2020;72(2):262-276.
4. Zhong JH, Ke Y, Gong WF, *et al.* Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014;260(2):329-340.
5. Kokudo T, Hasegawa K, Matsuyama Y, *et al.* Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65(5):938-943.
6. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-699.
7. Yao FY, Ferrell L, Bass NM, *et al.* Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. Hepatol Baltim Md 2001;33(6):1394-1403.
8. Wagle P, Narkhede R, Desai G, *et al.* Surgical management of large hepatocellular carcinoma: The first single-center study from Western India. Arq Bras Cir Dig ABCD 2020;33(2):1-7.
9. Wang W, Wei C. Advances in the early diagnosis of hepatocellular carcinoma. Genes Dis 2020;7(3):308-319.
10. Allaire M, Goumard C, Lim C, *et al.* New frontiers in liver resection for hepatocellular carcinoma. JHEP Rep Innov Hepatol 2020;2(4):100134.
11. Zeng S, Li L, Hu Y, *et al.* Machine learning approaches for the prediction of postoperative complication risk in liver resection patients. BMC Med Inform Decis Mak 2021;21(1):371.
12. Sehrawat SS, Premkumar M. Critical care management of acute liver failure. Indian J Gastroenterol 2024;43(2):361-376.
13. Wrighton LJ, O'Bosky KR, Namm JP, *et al.* Postoperative management after hepatic resection. J Gastrointest Oncol 2012;3(1):41-47.
14. Chen H, Jia W. Progress in hepatectomy for hepatocellular carcinoma and peri-operation management. Genes Dis 2020;7(3):320-327.
15. Zhou P, Chen B, Miao XY, *et al.* Comparison of FIB-4 index and Child-Pugh score in predicting the outcome of hepatic resection for hepatocellular carcinoma. J Gastrointest Surg 2020;24(4):823-831.
16. Amin MB, Greene FL, Edge SB, *et al.* The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67(2):93-99.
17. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 1999;19(3):329-338.
18. Yanaga K, Takenaka K, Yamamoto K, *et al.* Cardiac complications after hepatic resection. Br J Surg 1996;83(10):1448-1451.
19. Reznicek E, Sasaki K, Montane B, *et al.* Outcomes of liver transplantation in patients with preexisting coronary artery disease. Transplantation 2023;107(4):933-940.
20. Bolat D, Gunlusoy B, Aydogdu O, *et al.* Comparing the short-term outcomes and complications of monopolar and bipolar transurethral resection of bladder tumors in patients with coronary artery disese: A prospective, randomized, controlled study. Int Braz J Urol 2018;44(4):717-725.
21. Wan SZ, Nie Y, Zhang Y, *et al.* Assessing the prognostic performance of the Child-Pugh, model for end-stage liver disease, and albumin-bilirubin scores in patients with decompensated cirrhosis: A large Asian cohort from gastroenterology department. Dis Markers 2020;2020:5193028.
22. Tanemura A, Mizuno S, Maeda K, *et al.* Resection type is a predictor of postoperative complications in laparoscopic partial liver resection. Surg Endosc 2022;36(12):9054-9063.
23. Clavien PA, Barkun J, De Oliveira ML, *et al.* The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg 2009;250(2):187-196.
24. Kuramitsu K, Fukumoto T, Kobayashi T, *et al.* The Incidence of posthepatectomy liver failure defined by the international study group of liver surgery among living donors. J Gastrointest Surg 2016;20(4):757-764.
25. Al-Alem F, Mattar RE, Fadl OA, *et al.* Morbidity, mortality and predictors of outcome following hepatectomy at a Saudi tertiary care center. Ann Saudi Med 2016;36(6):414.

26. Magnin J, Bernard A, Cottenet J, *et al.* Impact of hospital volume in liver surgery on postoperative mortality and morbidity: Nationwide study. Br J Surg 2023;110(4):441-448.
27. Syaiful RA, Mazni Y, Siagian NKP, *et al.* Surgical resection for hepatocellular carcinoma: A single-centre's one decade of experience. Ann Med Surg 2012 2024;86(3):1289-1296.
28. Tendean M, Mambu TDB, Tjandra F, *et al.* Liver resection profile in Prof. Dr. R.D. Kandou general hospital: 1-year experience. Bali Med J 2021;10(1):47-52.
29. Wu J, Chan YT, Lu Y, *et al.* The tumor microenvironment in the postsurgical liver: Mechanisms and potential targets of postoperative recurrence in human hepatocellular carcinoma. Med Res Rev 2023;43(6):1946-1973.
30. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391(10127):1301-1314.
31. Benedetti Cacciaguerra A, Görgec B, Cipriani F, *et al.* Risk factors of positive resection margin in laparoscopic and open liver surgery for colorectal liver metastases: A new perspective in the perioperative assessment: A European multicenter study. Ann Surg 2022;275(1):e213-e221.
32. You D Do, Kim DG, Seo CH, *et al.* Prognostic factors after curative resection hepatocellular carcinoma and the surgeon's role. Ann Surg Treat Res 2017;93(5):252-259.
33. Ruiz E, Rojas Rojas T, Berrospi F, *et al.* Hepatocellular carcinoma surgery outcomes in the developing world: A 20-year retrospective cohort study at the National Cancer Institute of Peru. Heliyon 2016;2(1):e00052.
34. Longchamp G, Labgaa I, Demartines N, *et al.* Predictors of complications after liver surgery: A systematic review of the literature. HPB 2021;23(5):645-655.
35. Elfrink AKE, Olthof PB, Swijnenburg RJ, *et al.* Factors associated with failure to rescue after liver resection and impact on hospital variation: A nationwide population-based study. HPB 2021;23(12):1837-1848.
36. LiverGroup.org Collaborative. Outcomes of elective liver surgery worldwide: A global, prospective, multicenter, cross-sectional study. Int J Surg Lond Engl 2023;109(12):3954-3966.
37. Gavriilidis P, Hammond JS, Hidalgo E. A systematic review of the impact of portal vein pressure changes on clinical outcomes following hepatic resection. HPB 2020;22(11):1521-1529.
38. Lei GY, Shen L, Junnarkar SP, *et al.* Predictors of 90-day mortality following hepatic resection for hepatocellular carcinoma. Visc Med 2021;37(2):102-109.
39. Bodur MS, Tomas K, Topaloğlu S, *et al.* Effects of intraoperative blood loss during liver resection on patients' outcome: A single-center experience. Turk J Med Sci 2021;51(3):1388-1395.
40. Baumgartner R, Gilg S, Björnsson B, *et al.* Impact of post-hepatectomy liver failure on morbidity and short- and long-term survival after major hepatectomy. BJS Open 2022;6(4):zrac097.
41. Vitello DJ, Shah D, Ko B, *et al.* Establishing the clinical relevance of grade A post-hepatectomy liver failure. J Surg Oncol 2024;129(4):745-753.
42. Santambrogio R, Kluger MD, Costa M, *et al.* Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: Is clinical evidence of portal hypertension a contraindication? HPB 2013;15(1):78-84.
43. Bressan AK, James MT, Dixon E, *et al.* Acute kidney injury following resection of hepatocellular carcinoma: Prognostic value of the acute kidney injury network criteria. Can J Surg 2018;61(5):E11.
44. Lim C, Audureau E, Salloum C, *et al.* Acute kidney injury following hepatectomy for hepatocellular carcinoma: Incidence, risk factors and prognostic value. HPB 2016;18(6):540-548.
45. Merolle L, Marraccini C, Di Bartolomeo E, *et al.* Postoperative patient blood management: Transfusion appropriateness in cancer patients. Blood Transfus 2020;18(5):359-365.
46. Madhok B, Nanayakkara K, Mahawar K. Safety considerations in laparoscopic surgery: A narrative review. World J Gastrointest Endosc 2022;14(1):1-16.
47. Burke JR, Downey C, Almoudaris AM. Failure to rescue deteriorating patients: A systematic review of root causes and improvement strategies. J Patient Saf 2022;18(1):e140-e155.