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ORIGINAL ARTICLE

Impact of postoperative mean arterial pressure on the incidence of postoperative complications after hepatic resection for primary liver malignancy

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Abstract

Purpose We conducted this study to evaluate the impact of the postoperative mean arterial pressure (MAP) on surgical complications after hepatic resection.

Methods The subjects of this study were 199 patients who underwent hepatic resection for primary liver malignancy between 2004 and 2013. A clinically relevant postoperative complication was defined as a Clavien–Dindo grade ≥ III complication.

Results Based on an MAP cut-off value of 81.1 mmHg, the patients were grouped as follows: low MAP on both postoperative days (PODs) 1 and 2 (continuously low MAP), normal MAP on both PODs 1 and 2 (normal MAP), and others (transiently low MAP). The continuously low MAP group had the highest incidence of complications and the normal MAP group had the lowest incidence of complications compared with the expected incidence for this cohort ($p < 0.01$ and $p = 0.01$, respectively). Multivariate analysis revealed that both a continuously and transiently low MAP were independent predictors of postoperative complications ($p = 0.03$ and $p < 0.01$, respectively). Among the subtypes of complications, a low MAP had a significant relationship with ascites/pleural effusion and respiratory complications ($p < 0.01$ and $p = 0.03$, respectively).

Conclusions A low MAP on POD 1 and/or 2 is an independent predictor of postoperative complications.

Keywords Liver · Resection · Postoperative complication · Blood pressure

Introduction

Hepatic resection is a curative therapeutic option for liver malignancy [1]. Although the safety of hepatic resection has improved with advances in surgical techniques and perioperative management [2], hepatic resection is still associated with a high rate of postoperative complications, especially in patients with abnormal liver conditions such as viral hepatitis or liver fibrosis [3, 4]. These chronic liver diseases can lead to hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and mixed-type HCC and CC [5, 6]. Hepatic resection in such patients can be challenging and is accompanied by a high risk of operative mortality and morbidity [7].

The mean arterial pressure (MAP) is the driving pressure of tissue blood perfusion, and arterial hypotension is associated with poor circulation and tissue hypoperfusion [8]. Therefore, the MAP is reportedly used as a surrogate marker of the degree of blood perfusion in human organs [9–12]. Although the occurrence and duration of intraoperative hypotension are recognized as predictive factors for postoperative complications [10, 11, 13], the impact of postoperative hypotension on adverse effects is still uncertain. We analyzed patients who underwent hepatic resection in an attempt to establish the level and duration of postoperative MAP associated with postoperative complications. Because chronic liver disease decreases systemic vascular resistance and sensitivity to vasopressors, which may change postoperative hemodynamics [14, 15], this study studied the impact of MAP on the postoperative clinical course of patients with liver tumors associated with chronic liver damage, including HCC, CC, and mixed-type HCC and CC.

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Methods

Patients

We reviewed the medical records of 245 consecutive patients who underwent hepatic resection at Tottori University Hospital between January, 2004 and December, 2013. Among these, 199 patients with primary hepatic malignancies, including HCC, CC, and mixed-type HCC and CC, were enrolled in this study (Fig. 1). Since the MAP on postoperative days (PODs) 1 and 2 was used to predict postoperative complications, based on an analysis of the clinical course of the MAP, two patients who suffered complications within the first two PODs were excluded from the later analysis (Fig. 1). The operative indications were a performance status of < 3, preserved liver function (as evaluated by both an indocyanine green test and volumetric computed tomography), and good general condition without serious organ failure. Patients who had undergone hepatic resection combined with other local therapies, such as radiofrequency ablation and microwave coagulation therapy during laparotomy, were included, but those who had undergone liver transplantation, vascular reconstruction, bile duct reconstruction, lymph node dissection, and combined resection of another organ than the liver were excluded because of the expected higher complication rate than for simple hepatic resection. Nonanatomical resection was performed for patients thought to have an insufficient volume of remnant liver or those who had peripherally located tumors. Intraoperative temporary inflow clamping and transfusion were performed as necessary, based on the decision of the surgeons and/or anesthesiologists in charge. The patients were divided into three groups according to the average MAP: a continuously low MAP group (low daily average MAP on both PODs 1 and 2), a transiently low MAP group (low daily average MAP on only POD 1 or 2), and a normal MAP group (normal average MAP on both PODs 1 and 2). This study was approved by our institutional review board (Institutional Review Board approval number: 1606A029).

Measurement of arterial pressure

All patients underwent invasive arterial pressure monitoring until 8:00 am on POD 1. Subsequent invasive monitoring was performed only if instructed by the physician in charge. We obtained the arterial pressure measurements from the medical records, but measurements obtained from invasive monitoring took precedence over those obtained from noninvasive monitoring. The measurement obtained the day before surgery was used as the preoperative arterial pressure. For the arterial pressure measured on PODs 1–5, we used the measurements recorded each day, but

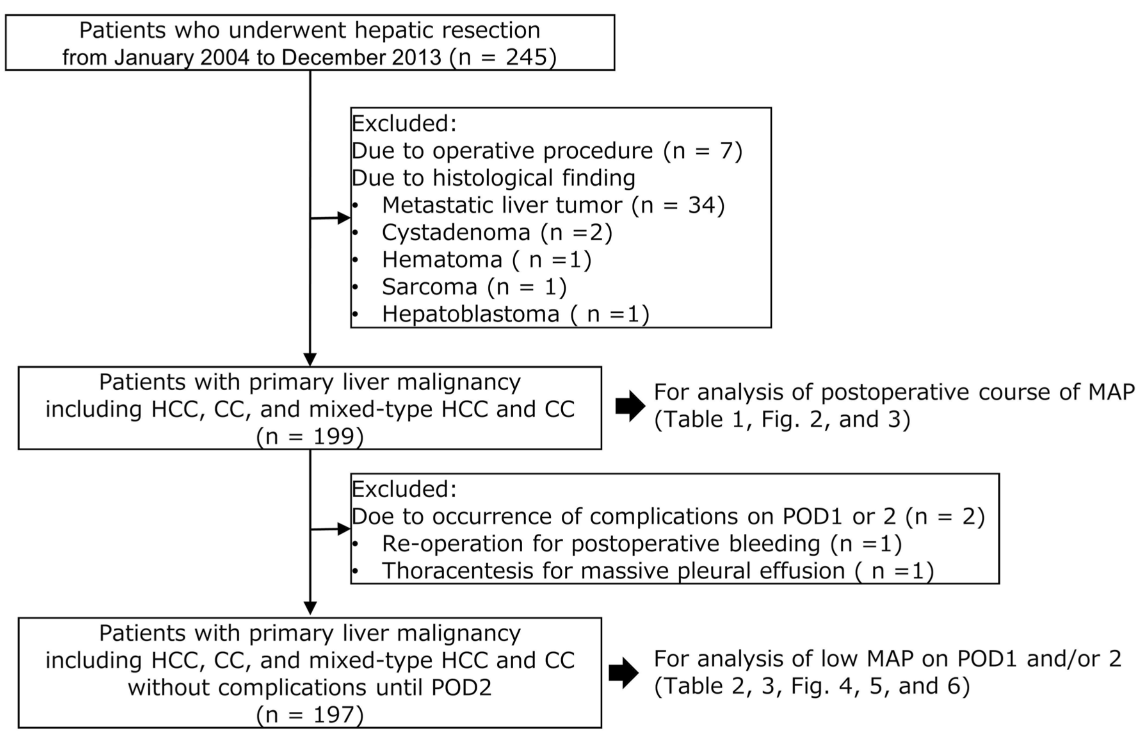


Fig. 1 Overview of the study cohort. Finally, 199 patients were eligible for inclusion

excluded values obtained within 30 min after the former pressure measurement. Thus, a maximum of 48 measurements per day were averaged. The MAP was calculated using the following formula: MAP = [(2 × diastolic pressure) + systolic pressure]/3.

Other variables

Other data included patient characteristics; namely, age, sex, body mass index, comorbidities, cause of hepatitis, Child–Pugh score, Model for End-Stage Liver Disease score, serum creatinine, and albumin; tumor characteristics; namely, the number of tumors and maximum tumor diameter; intraoperative data; namely, extent of resection, use of intermittent total hepatic inflow clamping, duration of surgery, intraoperative hemorrhage volume, intraoperative blood transfusion rate, length of hospital stay after surgical resection, and postoperative complications; and pathological findings; namely, the stage of fibrosis in the adjacent liver according to the Histological Activity Index [16]. Postoperative complications were defined as clinical Clavien–Dindo grade ≥ IIIa complications [17]. The comorbidity of cardiovascular disease was defined as a history of angina pectoris or chronic heart failure. Major resection was defined as hepatectomy involving more than two Couinaud segments.

Statistical analysis

Predictive factors of postoperative complications were investigated using multivariate analysis based on the variables selected by each univariate analysis using a logistic regression model. The predictive value of the MAP for postoperative complications was evaluated by a receiver operating characteristic (ROC) analysis. DeLong's test for two correlated ROC curves was used to compare the area under the curve. All continuous values are presented as means ± standard deviation. Welch's two-sample *t* test and one-way analysis of variance were used to compare continuous variables in two and more than three groups, respectively. For multiple comparisons of paired- and unpaired-pairwise continuous variables, the Dunnett method [18] and Holm method [19] were used to prevent erroneous inference, respectively. Correlations between preoperative and postoperative MAP were evaluated using Pearson's correlation test. Statistical analysis was conducted using the Chi-square test and Fisher's exact test (containing < 5 variables) for categorical variables. Residual analysis was used to identify the specific group with the greatest contribution to the Chi-square test result. A p value of < 0.05 was considered significant. R version 3.1.3 software (http://www.r-project.org/) was used for comparative statistical analysis.

Results

Postoperative complications developed in 52 (26.1%) of the 199 patients (Table 1). Figure 2 shows the systolic, mean, and diastolic arterial blood pressure of the 199 patients, both preoperatively and postoperatively. Pairwise testing revealed that the MAP on POD 1 (MAP^{POD1}) was significantly lower than the preoperative MAP. Therefore, MAP^{POD1} was used to determine the cut-off value of the MAP. The systolic arterial pressure was significantly higher on PODs 3 and 4 than preoperatively, and the MAP returned to the preoperative level on POD 5. Figure 3 shows the relationship between the preoperative and postoperative MAPs. Figure 2a, b shows that the preoperative MAP was weakly correlated with the MAP on both POD 1 and 2 ($r = 0.320$ and 0.335, respectively), with moderate correlations between the preoperative MAP and the MAPs on PODs 3, 4, and 5 ($r = 0.428$, 0.477, and 0.515, respectively). Therefore, MAP^{POD1} and MAP^{POD2} were selected for subsequent analysis of the association between the MAP and postoperative complications.

Next, using ROC analysis, the cut-off value of MAP^{POD1} was calculated to be 81.1 mmHg (Fig. 4). Based on this cut-off value, the patients were divided into three groups according to the MAP^{POD1} and MAP^{POD2} values: a normal MAP group, in which both MAP^{POD1} and MAP^{POD2} were no less than the cut-off value; a continuously low MAP group, in which both MAP^{POD1} and MAP^{POD2} were less than the cut-off value; and a transiently low MAP group, which comprised the remaining patients (Fig. 5a). Table 2 summarizes the clinical characteristics of the patients in this study. Patients with postoperative transient or continuously low MAP had significantly greater intraoperative blood loss

Table 1 Details of grade ≥ IIIa postoperative complications ($n = 52$)[a]

Complication	No. of patients
Death	
Multiple organ failure	1
Infectious complications	
Abdominal abscess	12
Pneumonia	1
Thoracic empyema	1
Liver-specific complications	
Ascites and/or pleural effusion	20 (1)
Bile leakage/bile stricture	20
Other complications	
Pulmonary complication other than pneumonia	2
Others	2 (1)

Numbers in parentheses indicate the number of patients whose complication occurred within 2 days after surgery

[a]Some patients had more than one complication

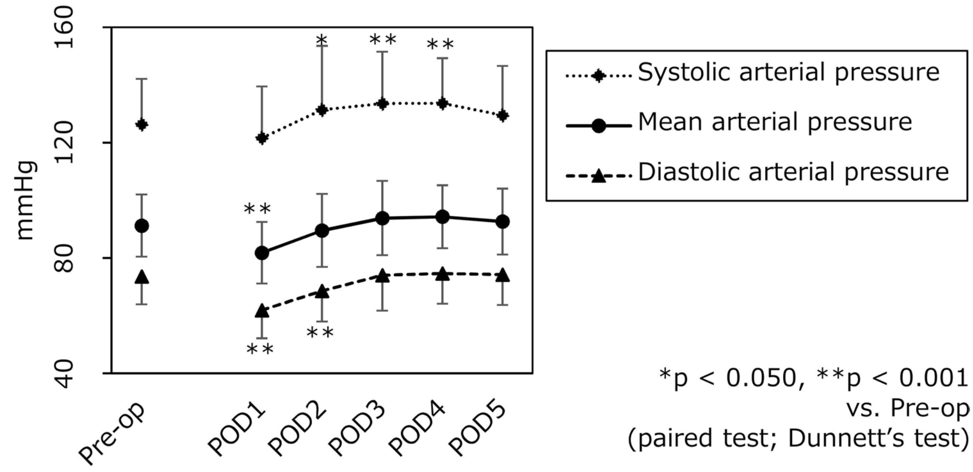
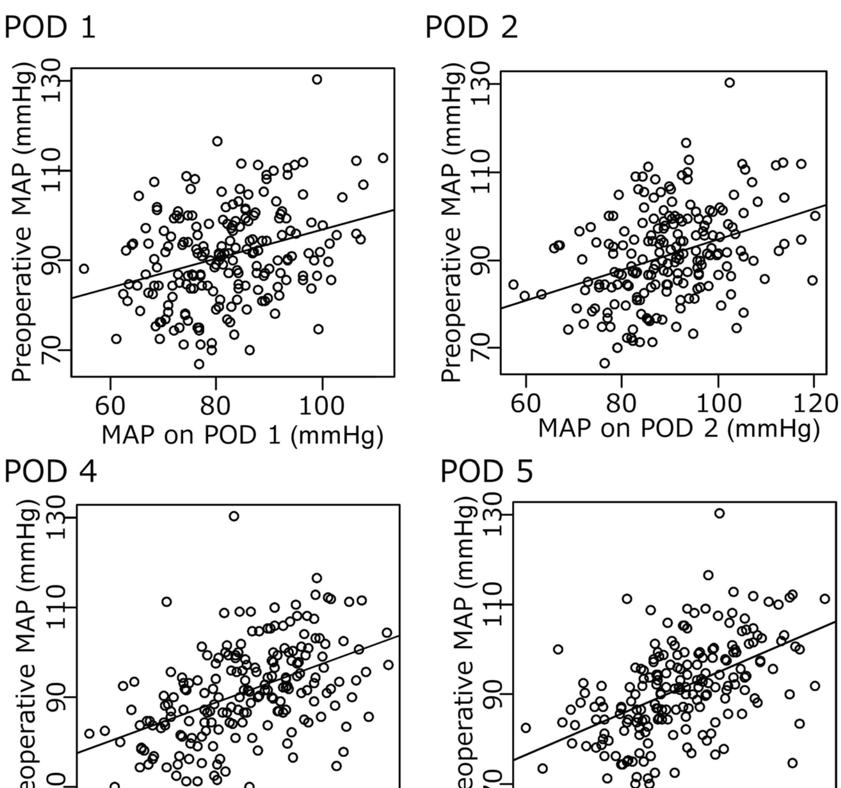


Fig. 2 Arterial pressure during hepatic resection. Compared with the preoperative data, the mean arterial pressure was significantly lower on POD 1 and the diastolic pressure was lower on PODs 1 and 2, whereas the systolic pressure was significantly higher on PODs 2, 3, and 4. *Pre-op* the day before surgery, *POD* postoperative day



	Pearson's correlation	
	r	p value
POD1	0.321	<0.001
POD2	0.334	<0.001
POD3	0.428	<0.001
POD4	0.477	<0.001
POD5	0.515	<0.001

Fig. 3 Correlations between the mean arterial pressure (MAP) preoperatively and on each POD. Weak correlations were found between the preoperative MAP and the MAP on PODs 1 and 2, whereas moderate correlations were observed between the preoperative MAP and the MAP on PODs 3, 4, and 5. *MAP* mean arterial pressure, *POD* postoperative day

and longer operative duration ($p = 0.004$ and 0.001, respectively). Moreover, multiple comparisons revealed that the continuously low MAP group had a significantly longer operative duration than the other two groups ($p = 0.014$, adjusted p value). The ROC curves of the combination of MAP^{POD1} and MAP^{POD2} showed a sensitivity of 28.3% and a specificity of 94.5% in the continuously low MAP group for the development of postoperative complications (area under the curve 0.6257) (Fig. 5b). The accuracy of predicting postoperative complications was improved further by combining

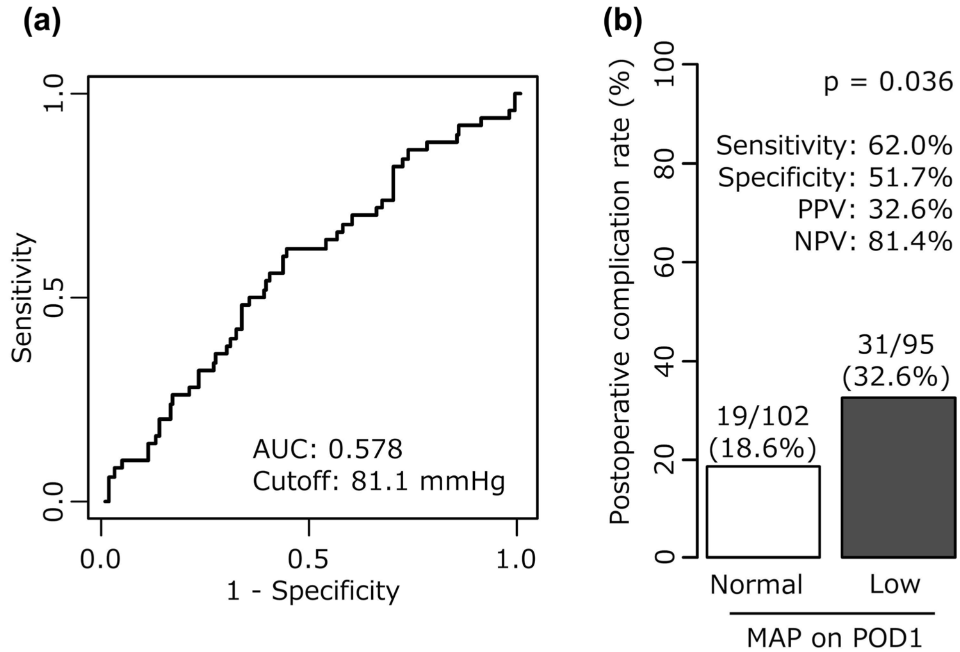


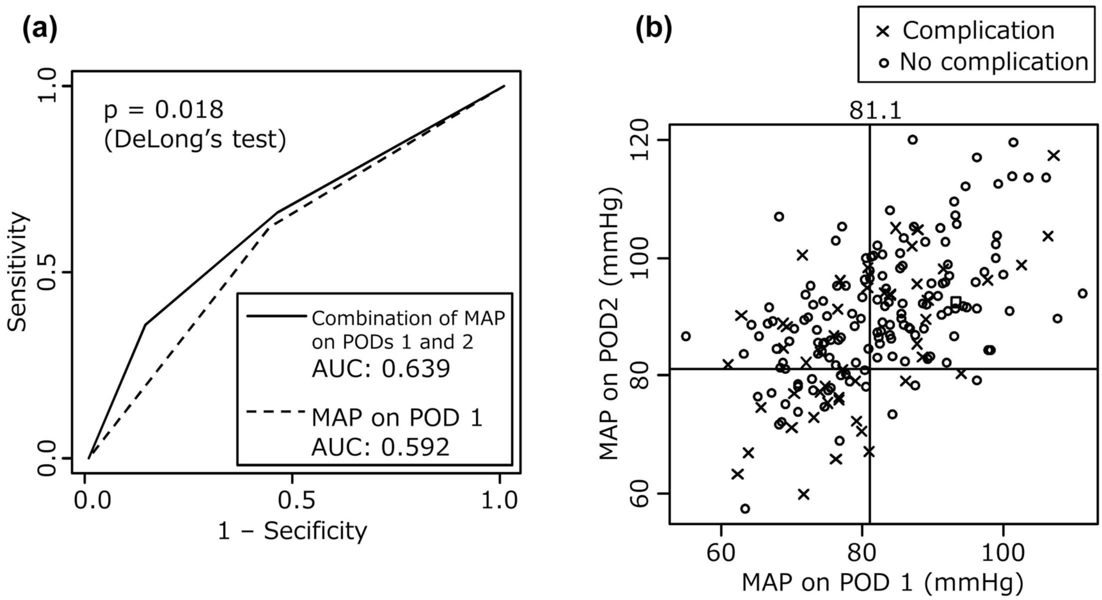
Fig. 4 **a** Receiver operating characteristics analysis of the mean arterial pressure (MAP) on POD 1 for postoperative complications. The cut-off value of the MAP was 81.1 mmHg. **b** The cut-off value showed 61.5% sensitivity and 56.3% specificity. *AUC* area under the curve, *MAP* mean arterial pressure, *NPPV* negative predictive value, *POD* postoperative day, *PPV* positive predictive value

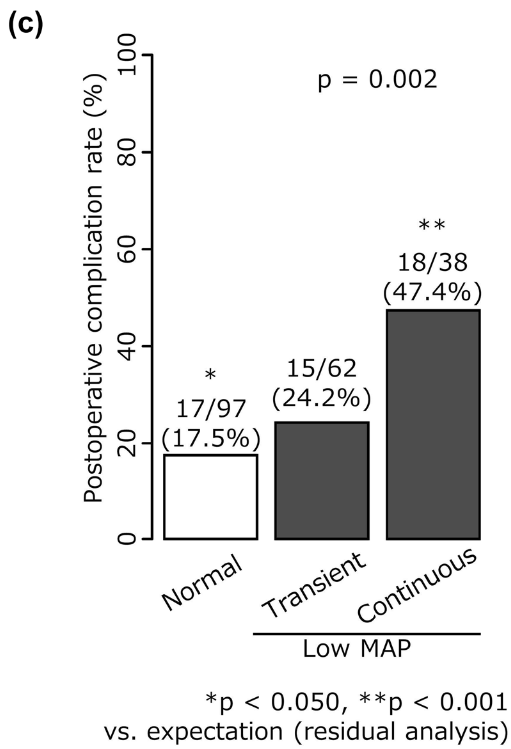
MAP^{POD1} and MAP^{POD2} vs only MAP^{POD1} ($p=0.018$). Compared with the expected incidence of complications in this cohort, the normal MAP group had a significantly lower incidence, whereas the continuously low MAP group had a significantly higher incidence ($p=0.014$ and $p<0.001$, respectively, in the residual analysis of the Chi square test) (Fig. 5c, d). Thus, these three groups showed significantly different frequencies of postoperative complications based on their 2-day MAP values. Table 3 shows the results of the multivariate analysis of the prediction of postoperative complications. Continuously low MAP was an independent risk factor for postoperative complications. In contrast, transiently low MAP, a long operative duration, and intraoperative major bleeding had a less significant relationship with complications. With respect to the types of complications, a postoperative continuously low MAP was significantly associated with abnormal fluid accumulation and respiratory complications (Fig. 6).

Discussion

The present study found that patients with a low MAP on POD 1 and/or 2 had an increased probability of postoperative complications. The highest incidence of complications occurred when a low MAP persisted during both PODs 1 and 2. These data suggest that hypotension in the acute postoperative phase may reflect insufficient blood flow in organs and circulatory dysfunction, with a subsequent increased risk of postoperative complications.

Complications after hepatic resection are common, with morbidity rates ranging from 30.9 to 42.6% [20, 21]. Similar to previous studies, grade ≥ IIIa complications were observed in 26% of the patients who underwent hepatic resection in our study. Patients with a postoperative MAP lower than 81.1 mmHg had a high complication rate. The cut-off value of MAP in this study was higher than what has been reported in other studies as the acute clinical phase blood pressure [10–13, 22]. For example, the Surviving Sepsis Campaign Guideline recommended an MAP of ≥ 65 mmHg in patients with hypoperfusion caused by sepsis [12]. Another study recommended a cut-off MAP of 60 mmHg during anesthesia for cardiovascular surgery [11]. However, these studies targeted patients whose low arterial pressures were assumed to be caused by different conditions such as septic shock or anesthesia. Hence, these cut-off values for MAP may not be applicable to patients on POD 1 and 2 after liver surgery. In fact, only eight (4.0%) patients had an MAP lower than 65 mmHg on POD1 in this study. In one study on hepatic disorders, a similar target value of MAP (83.32 mmHg) was reported for the prediction of ascites in patients with hepatitis C virus-related cirrhosis [9]. This report was consistent with our findings in patients after hepatic resection. In the present study, an MAP of 81.1 mmHg as a cut-off value on POD 1 and 2 was suitable for the prediction of postoperative, mainly liver-related, complications. This indicates that a relatively high MAP might be needed to maintain the circulation in the liver rather than mainly in critical organs such as the brain or kidney, which could be protected from systemic hypotension by the autoregulation of regional perfusion [23].





(d)

	Low MAP duration (day)	
	≥1	2
Sensitivity (%)	66.0	36.0
Specificity (%)	50.8	80.7
PPV (%)	33.0	47.4
NPPV (%)	82.5	78.9

Fig. 5 **a** Receiver operating characteristics analyses using a mean arterial pressure (MAP) of 81.1 mmHg as the cut-off value. The predictive accuracy was improved with a combination of MAP on PODs 1 and 2 for postoperative complications ($p=0.025$). **b** Plots showing patients' profiles of MAP values and the presence or absence of complications. **c** The continuously low MAP group had a significantly higher incidence of postoperative complications ($p<0.001$), whereas the normal MAP group had a significantly lower incidence ($p=0.014$). **d** A transiently or continuously low MAP predicted postoperative complications with an 81% NPV, and a continuously low MAP on PODs 1 and 2 predicted postoperative complications with a 47% PPV. *AUC* area under the curve, *MAP* mean arterial pressure, *NPPV* negative predictive value, *POD* postoperative day, *PPV* positive predictive value

Table 2 Comparison of clinicopathological features depending on postoperative mean arterial pressure

		Status of postoperative mean arterial pressure			*p* value	*p* value[e]
		Normal ($n = 97$)	Transient low ($n = 62$)	Continuous low ($n = 38$)		
Demographic data						
Age (years)	67.8 ± 10.0	67.5 ± 10.4	68.3 ± 9.3	68.6 ± 11.2	0.387	
Sex (%), male/female	165 (84)/32 (16)	87 (90)/10 (10)	49 (79)/13 (21)	29 (76)/9 (24)	0.079	
BMI (kg/m^2)	23.1 ± 3.0	23.3 ± 3.0	22.8 ± 2.9	22.6 ± 3.1	0.061	
Cause of hepatitis (%), HBV/HCV	74 (38)/62 (32)	35 (36)/32 (33)	27 (43)/11 (18)	12 (32)/13 (34)	0.255	
Child–Pugh score (%), A/B	185 (94)/12 (6)	91 (94)/6 (6)	57 (92)/5 (8)	37 (97)/1 (3)	0.543	
MELD score	7.8 ± 1.4	7.9 ± 1.5	7.7 ± 1.0	7.7 ± 1.2	0.207	
Creatinine (mg/dl)	0.77 ± 0.19	0.78 ± 0.20	0.75 ± 0.19	0.74 ± 0.20	0.113	
Albumin (g/dl)	3.9 ± 0.5	3.9 ± 0.5	3.8 ± 0.4	3.9 ± 0.5	0.988	
Comorbidities (%)						
Hypertension[a]	85 (43)	47 (48)	27 (44)	11 (29)	0.120	
Diabetes	66 (34)	33 (34)	21 (34)	12 (32)	0.962	
Cardiac disease[b]	21 (11)	10 (10)	5 (8)	6 (16)	0.535	
Cigarette smoking (current or past)	126 (64)	65 (67)	35 (56)	26 (68)	0.327	
Operative data						
Extent of hepatic resection (%)						
Non-anatomical	89 (45)	47 (48)	30 (48)	12 (32)	0.172	
Major resection	54 (27)	24 (25)	16 (26)	14 (37)	0.345	
Combined with RFA	23 (12)	14 (14)	7 (11)	2 (5)	0.326	
Blood loss (ml)	820.4 ± 1207.9	785.6 ± 1210.8	897.4 ± 1207.6	1228.5 ± 2009.4	0.004	0.273
Blood transfusion (%)	68 (35)	29 (30)	20 (32)	19 (50)	0.094	
Operative duration (min)	422.0 ± 157.7	423.8 ± 153.2	402.2 ± 155.0	486.5 ± 188.9	0.001	0.014
Inflow clamping (%)	98 (50)	41 (42)	35 (56)	22 (58)	0.117	
Intraoperative fluid balance	3206.6 ± 1580.4	3171.0 ± 1474.4	3283.9 ± 1763.6	3282.9 ± 1476.6	0.537	
Hospital stay (days)	31.1 ± 41.4	31.1 ± 35.5	31.3 ± 52.3	39.1 ± 42.6	0.173	
Pathological data						
Pathological diagnosis[c], HCC/mixed/CC	180 (91)/4 (2)/13 (7)	90 (93)/1 (1)/6 (6)	58 (93)/1 (2)/3 (5)	32 (84)/2 (5)/4 (11)	0.412	
Number of tumors (%), single/multiple	150 (76)/47 (24)	75 (77)/22 (23)	45 (72)/17(28)	30 (79)/8 (21)	0.715	
Diameter of tumor (cm)	4.5 ± 3.7	4.4 ± 3.7	4.5 ± 3.8	5.3 ± 5.1	0.103	
Liver cirrhosis[d] (%)	64 (32)	38 (39)	17 (27)	9 (24)	0.136	

Data are presented as *n* (%) or mean ± standard deviation

BMI body mass index, *MELD* model for end-stage liver disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *RFA* radiofrequency ablation, *HCC* hepatocellular carcinoma, *CC* cholangiocarcinoma

[a]Defined as preoperative hypertension requiring antihypertensive medication

[b]Defined as a history of ischemic heart disease and/or chronic heart disease

[c]Diagnosed with resected specimens

[d]According to histology activity index (HAI) and fibrosis (stage) by Ishak classification

[e]Pairwise comparison between "transient low MAP" group and "continuous low MAP" group using Holm method for adjustment

Another important finding of this study is that continuously low MAP on PODs 1 and 2 had a worse effect on short-outcomes than transiently low MAP. Although continuously low MAP was associated with long operative duration, which may indicate major surgical invasion ($p = 0.014$ vs normal MAP, $p = 0.008$ vs transient low MAP; Table 2), there was no correlation between the operative duration of the transiently low MAP group and the normal MAP group ($p = 0.901$). Both the continuously and transiently low MAP groups had higher rates of postoperative complications than the normal MAP group, suggesting that postoperative low arterial pressure itself may adversely affect short-term

Table 3 Significant factors predictive of postoperative complications

Variables	Postoperative complications ($n=50$)			
	Univariate	Multivariate		
	p value	HR	95% CI	p value
Age, ≥ 75 years	0.726			
Sex, male	0.089			
BMI, ≥ 25 kg/m^2	0.776			
Child–Pugh score, ≥ B	0.975			
MELD score, ≥ 8	0.111			
Smoke, yes	0.731			
Comorbidities				
HTN	0.676			
DM	0.772			
Cardiac disease	0.167			
Hepatectomy				
Major	0.045	1.230	0.560–2.647	0.600
Non-anatomical	0.133			
Combined with RFA	0.670			
Intraoperative bleeding, ≥ 1000 ml	0.012	1.230	0.497–2.976	0.648
Fluid balance, ≥ 4000	0.039	1.414	0.570–3.450	0.448
Operative duration, ≥ 6 h	0.002	2.512	1.080–6.177	0.037
Total inflow clamping, yes	0.178			
No. of tumors, multiple	0.978			
Diameter of tumor, ≥ 5 cm	0.067			
Cirrhosis, yes	0.434			
Low MAP[a]				
≥ 1 day	0.014	2.124	1.072–3.025	0.033
2 days	0.001	3.211	1.468–7.040	0.003

Results based on logistic regression models with binomial data

MAP mean arterial pressure, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *MELD* model for end-stage liver disease, *HTN* hypertension, *DM* diabetes mellitus, *RFA* radiofrequency ablation

[a]Each population based on the duration of low MAP were analyzed separately in different multivariable models

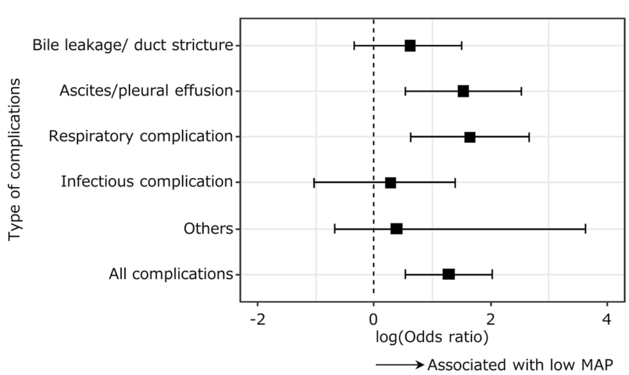


Fig. 6 Odds ratios of a low mean arterial pressure (MAP) for the types of complications. Ascites/pleural effusion and respiratory complications were well correlated with a low postoperative MAP. *MAP* mean arterial pressure

outcome, in addition to major surgical invasion. Other studies similarly showed that a longer duration of low MAP during surgery was associated with a higher incidence of postoperative complications [10, 22]. Maintaining the MAP during the postoperative clinical course can be achieved with sufficient infusion and/or dopamine use, which increases the MAP and cardiac output through an increase in the stroke volume and heart rate. These findings imply that the outcomes of patients with a low MAP on POD 1 might be improved by maintaining the MAP on the following days if a continuously low MAP directly worsens the patient's outcome through persistent hypoperfusion.

How does the postoperative low MAP trigger the development of complications? Intravascular volume derangements, hypovolemia, and hypervolemia are all associated with increased postoperative morbidity [24]. On one hand, hypovolemia leads to decreased tissue perfusion, which can result in multiorgan failure [25]. On the other hand, hypervolemia also causes tissue perfusion through edema and has deleterious effects on various organ systems, leading to ascites, pulmonary complications, acute kidney injury, and poor wound hearing, including anastomotic dehiscence in the gastrointestinal tract [24, 26]. Because arterial pressure has been used to provide intravascular volume status, it is possible that patients with low arterial pressure may have intravascular abnormality and need additional treatment such as intravenous fluid or vasoconstriction. It is also possible that low MAP is caused by decreased sensitivity for endogenic vasopressor and decreased systemic vascular resistance, because of the liver damage. Patients with liver damage have a characteristic hemodynamic circulation such as systemic vasodilation and portal hypertension, mainly related to reduced nitric oxide [14]. Therefore, patients whose systemic blood pressure responds badly to surgical invasion may have poor liver reserve and portal hypertension and are at increased risk of hepatic complications.

Several limitations of this study must be mentioned. First, cardiac dysfunction that may cause hypotension, such as arrhythmia and cardiac failure, were not taken into account in this study; therefore, patients with primary cardiac failure might show a poor response to postoperative management. Second, specific modifiers of hypoperfusion, such as anemia, postoperative bleeding, and use of vasopressors and volume expanders, were not considered. Third, this was a retrospective observational study with a limited sample size, and it was impossible to consider all factors such as coexisting events and treatments that influence postoperative hemodynamics. To fully understand the etiology of hypotension and postoperative complications, these factors should be assessed in future studies. Therefore, although the results of this study indicate that hypotension is associated with postoperative complications, this should not be interpreted as a definitive conclusion. Further studies are needed to confirm the relationship between the MAP and postoperative complications. The effect of maintaining a stable MAP to prevent postoperative complications in patients with hepatic resection should also be examined in a prospective study.

In conclusion, a low postoperative MAP in patients with primary hepatic cancer might be a surrogate marker of circulatory dysfunction, which is related to an elevated risk of postoperative complications. Moreover, a continuously low MAP on PODs 1 and 2 was found to significantly increase the risk of postoperative complications. Therefore, closer observation is needed for these patients. Further prospective trials are warranted to establish if maintaining a stable MAP can help prevent postoperative complications.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

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