Bioelectrical impedance analysis for predicting postoperative complications and survival after liver resection for hepatocellular carcinoma

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Background: Bioelectrical impedance analysis provides information on body composition and nutritional status. However, it's unclear whether the preoperative edema index or phase angle predicts postoperative complication or mortality in patients with hepatocellular carcinoma (HCC). Thus, we investigated whether preoperative bioelectrical impedance analysis could predict postoperative complications and survival in patients with HCC.

Methods: Seventy-nine patients who underwent hepatectomy for hepatocellular carcinoma were prospectively enrolled and bioelectrical impedance analysis was performed before surgery. Postoperative ascites or acute kidney injury and patients' survival were monitored after surgery.

Results: Among 79 patients, 35 (44.3%) developed ascites or acute kidney injury after hepatectomy. In multivariate analysis, a high preoperative edema index (extracellular water/total body water) (>0.384) (odds ratio 3.96; 95% confidence interval: 1.03–15.17; P=0.045) and higher fluid infusion during surgery (odds ratio 1.36; 95% confidence interval: 1.04–1.79; P=0.026) were identified as significant risk factors for ascites or acute kidney injury after hepatectomy. Subgroup analyses showed that the edema index was a significant predictor of ascites or acute kidney injury in patients with cirrhosis. Tumor size was the only significant predictive factor for short-term survival after hepatectomy.

Conclusions: The preoperative edema index using bioelectrical impedance analysis can be used as a predictor of post-hepatectomy complication, especially in patients with liver cirrhosis.

Keywords: Hepatocellular carcinoma (HCC); hepatectomy; electrical impedance; postoperative complications

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Introduction

Liver cancer, including hepatocellular carcinoma (HCC), is the sixth most common cancer and the fourth leading cause of cancer death worldwide, with about 841,000 new cases and 782,000 deaths annually (1). It is mainly caused by damage to the liver parenchyma in patients with hepatitis due to viral infection or alcoholic liver disease. Hepatectomy is an effective HCC treatment option in patients who are not eligible for liver transplantation, and although recent advances in medicine have resulted in notable improvements in postoperative mortality (2,3), postoperative morbidity is still unsatisfactory (4). Ascites is one of the most common postoperative complications after liver resection, with an incidence of 12.1–41.7%, and may lead to postoperative dehydration, electrolyte imbalance, infection, dyspnea, and hepatic failure (5). In patients undergoing hepatectomy, postoperative ascites is associated with overall postoperative morbidity and acute renal failure, and requires special treatment (including albumin infusion, diuretics, and paracentesis) and prolonged hospital stay (6). Furthermore, postoperative ascites is associated with a high incidence of HCC recurrence and mortality (7). It occurs due to the imbalance between the portal venous inflow and the diminished hepatic venous outflow of the remnant liver and is associated with acute portal hypertension (8). Because the majority of patients undergoing hepatectomy for HCC suffer from underlying liver disease, this risk is increased. The risk factors for postoperative ascites include liver cirrhosis, low serum albumin, low platelet count, high indocyanine green level, notable blood loss, large tumor size, and red blood cell transfusion (6,7,9). Acute kidney injury (AKI) after hepatectomy is a well-known complication, with up to 15.1% incidence (10). AKI following hepatectomy is associated with short-term mortality (11,12). Known risk factors for AKI after hepatectomy include a high Model for End-stage Liver Disease score, the presence of non-dialytic chronic kidney disease, biliary obstruction in the preoperative period, perioperative hemodynamics instability, bleeding, and sepsis (13).

Bioelectrical impedance analysis (BIA) is a simple, noninvasive, reproducible technique for evaluating body water and composition (14). This technique measures the resistance, which is related to the composition of the tissues such as intracellular and extracellular water (15). This technique also measures the reactance and phase angle at 50 kHz. The results of BIA correlate with prognosis in various populations, including patients with cancer (16-18). Also, sarcopenia and phase angle detected by BIA is a negative prognostic factor in two studies (19,20). Recent studies have reported that various factors that can be measured by BIA in patients with various carcinomas are related to the prognosis. Yasui-Yamada *et al.* reported that the phase angle measured by BIA may play an important role in short term and long term postoperative prognosis in patients with gastrointestinal or hepatobiliary cancer (21). Barao *et al.* reported that the phase angle and patient-generated subjective global assessment were prognostic factors in patients with colorectal cancer (22). Additionally, Axelsson *et al.* reported that the phase angle at diagnosis and the standardized phase angle were significant factors for survival in patients with advanced head and neck cancer. Studies have also reported that various factors measured by BIA in patients with cirrhosis of the liver are associated with prognosis and morbidity (23). Recently, one study reported that sarcopenia and phase angle is a prognostic indicator for survival in cirrhotic patients with HCC (24). Another study reported that the edema index (extracellular water/total body water) increases with hepatic dysfunction in liver cirrhosis, and the incidence of ascites is higher when the edema index is greater than 0.398 in patients with cirrhosis (25). The presence of sarcopenia is associated with the occurrence of cirrhotic complications and poor prognosis (19); therefore, confirming that the presence of sarcopenia may be clinically important information that can be obtained via BIA. However, to our knowledge, no study has examined whether the preoperative edema index or phase angle predicts postoperative complication or mortality in patients with HCC. Therefore, this study aimed to assess whether factors such as phase angle, presence of sarcopenia, and edema index, which can be measured through BIA, affect postoperative complications, including ascites and AKI, and prognosis after liver resection in patients with HCC. We present the following article in accordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5194).

Methods

Patients

We prospectively enrolled the patients who underwent hepatectomy for HCC at our hospital from July 2016 to June 2018. Inclusion criteria were patients over 19 years old scheduled to undergo liver resection for hepatocellular carcinoma. Exclusion criteria were: (I) patients who had previously received implantable electronic devices; (II) patients who had previously undergone liver transplantation; (III) patients who refused BIA. Diagnosis of underlying liver disease was confirmed by the histologic examination after hepatectomy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-OBS-16-287), and all patients provided informed consent.

BIA and definition of edema index

BIA was performed on the day of admission before intravenous hydration using a multi-frequency BIA InBody 770 scanner (InBody, Seoul, Republic of Korea). BIA was performed with patients in a standing position according to the manufacturer's instructions after shoes, coats, and sweaters had been removed. The BIA scanner used frequencies 1, 5, 50, 260, 500, and 1,000 kHz over 60 seconds. By BIA, phase angle, extracellular fluid and total body fluid, body cell mass, and appendicular skeletal muscle mass can be derived by computed analysis. Edema index can be calculated as the ratio of extracellular fluid to total body fluid. Sarcopenia was defined using height-adjusted appendicular skeletal muscle mass (appendicular skeletal muscle mass/height^2, kg/m^2), and was <7.0 kg/m^2 for men and <5.7 kg/m^2 for women according to a previous study involving Asians (26).

Surgical procedure

Patients with HCC were classified according to modified Union for International Cancer Control, and liver function was assessed by Child-Pugh score and indocyanine green 15' retention test (ICGR15). The surgery's extent was determined according to the judgment of the liver surgery team considering tumor location, stage, liver function, and performance status.

Definition of clinical outcome

We defined "postoperative ascites" as peak drainage of ascites >500 mL/day during hospitalization, or when patients needed diuretics to control ascites, according to previous study (5). AKI was defined according to the Kidney Disease Improving Global Outcomes guideline as follows: stage 1, a peak serum creatinine of 1.5–1.9 times baseline or ≥0.3 mg/dL (≥26.5 μmol/L) elevation; stage 2, a peak serum creatinine of 2.0–2.9 times baseline; and stage 3, a peak serum creatinine of >3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L) or initiation of renal replacement therapy (27). Liver cirrhosis and degree of hepatic fibrosis were defined by pathological reports after liver resection. Patients were followed until June 2018 for survival analysis.

Statistical analyses

The sample size was calculated via a review of previous studies. The incidence of ascites after hepatectomy was determined to be 10.3% based on previous study (5). In this study, Child-Pugh class C or severe preoperative complications in an HCC patient are considered contraindications for hepatic resection. Also, Major hepatic resection was considered for patients who had an ICGR15 of less than 20%. Because the subjects in this study and our study were similar, we estimated the incidence of postoperative ascites or AKI as 10.3% even though various incidences were reported in several studies. The incidence of ascites after hepatectomy has been reported to be 10.3% and the incidence of ascites is reported to be 4.04 times according to the edema index (25). When the incidence of ascites or AKI after hepatectomy according to edema index was analyzed using a multivariable logistic regression model, the required number of study subjects was calculated as 76, at a power of 80% and alpha of 0.05 (28). All data are presented as mean ± standard deviation or as numbers and percentages. Categorical variables were analyzed using the chi-square or Fisher's exact test. Quantitative data were analyzed using the independent *t*-test. Factors associated with the development of postoperative ascites or AKI were analyzed via binary logistic regression analysis. The area under the curve (AUC) was calculated for measuring overall ascites or AKI prediction accuracy of edema index. Cox proportional hazards analysis was used to identify factors associated with survival. Statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, Illinois, United States). A P value of <0.05 was considered statistically significant.

Table 1 Baseline characteristics of the study population

Characteristics	Total (N=79)	Patients with post-operative ascites or AKI (n=35)	Patients without post-operative ascites or AKI (n=44)	P value
Age (years)	56.1±10.9	57.3±11.0	55.1±10.8	0.382
Male gender	66 (83.5)	27 (77.1)	39 (88.6)	0.171
Liver cirrhosis	44 (55.7)	22 (62.9)	22 (50.0)	0.253
Etiology HBV/HCV/alcohol/etc.	65/2/2/10	28/0/1/6	37/2/1/4	0.376
Hemoglobin (g/dL)	14.0±1.8	13.6±2.1	14.3±1.4	0.110
Platelet (10^3/μL)	170.8±69.6	169.3±80.8	171.9±60.1	0.868
Creatinine (mg/dL)	0.97±0.95	0.85±0.20	1.06±1.25	0.331
Albumin (g/dL)	4.5±0.4	4.4±0.5	4.5±0.4	0.553
Bilirubin (mg/dL)	0.55±0.28	0.64±0.33	0.48±0.22	0.018
AST (U/L)	32.7±15.4	34.8±19.1	30.9±11.7	0.265
ALT (U/L)	35.1±19.5	35.6±24.0	34.7±15.2	0.841
INR	1.09±0.08	1.10±0.09	1.08±0.08	0.215
ICGR15 (%)	14.3±6.8	14.1±6.9	14.4±6.8	0.871
Number of HCC	1.3±1.1	1.3±1.5	1.2±0.7	0.596
HCC size (cm)	4.6±3.9	5.3±5.1	4.0±2.7	0.170
HCC stage (modified UICC) (I/II/III)	17/55/7 (21.5/69.6/8.9)	7/25/3 (20.0/71.4/8.6)	10/30/4 (22.7/68.2/9.1)	0.857
No. of resected segment (1/2/3/4/5)	17/31/15/14/2 (21.5/39.2/19.0/17.8/2.5)	4/15/6/9/2 (11.4/42.9/17.1/25.7/5.7)	13/17/9/5/0 (29.5/38.6/20.5/11.4/0.0)	0.014
Total body water (L)	36.32±5.90	35.37±6.20	37.08±5.60	0.202
Edema index[a]	0.384±0.007	0.387±0.008	0.381±0.006	<0.001
Body cell mass (kg)	32.08±5.40	31.09±5.69	32.86±5.08	0.148
BMI (kg/m^2)	23.7±3.3	23.7±3.8	23.7±2.9	0.964
Sarcopenia	9 (11.4)	4 (11.4)	5 (11.4)	1.000
Phase angle	5.41±0.76	5.11±0.80	5.65±0.63	0.001
Fluid infusion during operation (L)	3.57±2.07	4.27±2.45	3.03±1.55	0.013
Blood loss during operation (L)	1.04±1.22	1.16±1.23	0.94±1.22	0.438
Transfusion during operation (L)	0.66±1.16	0.86±1.29	0.50±1.04	0.170
Transfusion after operation (L)	0.31±0.75	0.49±0.96	0.16±0.49	0.075

Continuous variables are expressed as mean ± standard deviations and categorical variables are expressed as numbers (%). [a], edema index was calculated using extracellular water/total body water. AKI, acute kidney injury; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; ICGR15, indocyanine green 15' retention test; HCC, hepatocellular carcinoma; UICC, Union for International Cancer Control; BMI, body mass index.

Results

Baseline characteristics and surgical procedure

Seventy-nine patients were included in the study and their baseline characteristics are summarized in (*Table 1*). The mean patient age was 56.1±10.9 years, and 83.5% were men. Forty-four (55.7%) had liver cirrhosis. The mean HCC size was 4.6±3.9 cm, and 88.6% had only one

HCC. The mean preoperative ICGR15 was 14.3%±6.8%. Patients underwent various surgeries ranging from segmentectomy to lobectomy depending on tumor size and location. The number of resected segments were ranging from 1 to 5. The most frequent surgery was right lobectomy (14%). The median hospitalization duration was 16 (range, 10–45) days.

Incidence of postoperative ascites and AKI

Among the 79 patients, 35 (44.3%) and 4 (5.1%) developed postoperative ascites and AKI, respectively; 8, 19, and 8 patients had ascites <500, between 500–1,000, and >1,000 mL/day, respectively. Four cases of AKI were classified as grade I and II in 2 cases each. Three patients recovered during hospitalization. One patient with grade I AKI did not recover renal function during hospitalization, but fully recovered 1 month later. Four patients died during the median follow-up of 10.9 months; all of these experienced HCC recurrences and died because of disease progression.

Risk factors for postoperative ascites or AKI in all patients

In univariate analyses, a higher edema index, low phase angle, higher intraoperative fluid infusion, and more extensive surgery (higher number of resected segments) were significant risk factors for ascites or AKI in patients who underwent liver resection. However, liver cirrhosis and sarcopenia were not significant risk factors for postoperative ascites or AKI. Specifically, there was a significant difference in the mean values of the edema index (0.387 *vs.* 0.381, P<0.001) between the groups with and without ascites or AKI. Based on the median value of the edema index, the incidence of postoperative ascites or AKI was higher in patients with a high edema index (>0.384) than in those with a low edema index (≤0.384) (64.9% *vs.* 31.4%, P=0.001). In multivariate analysis, edema index >0.384 [odds ratio (OR) 3.96; 95% confidence interval (CI): 1.03–15.17; P=0.045] and higher fluid infusion during surgery (OR 1.36; 95% CI: 1.04–1.79; P=0.026) were significant risk factors for postoperative ascites or AKI (*Table 2*). The AUC of edema index was 0.712 (95% CI: 0.595–0.829; P=0.001) for predicting postoperative ascites or AKI (*Figure 1*). The edema index proved to be sensitive (68.6%) and specific (70.5%) when using cutoffs as edema index >0.384.

Risk factors for postoperative ascites or AKI in two subgroups (patients with and without liver cirrhosis)

We conducted a subgroup analysis to determine whether the edema index is useful in the presence of liver cirrhosis. Among the 44 cirrhotic patients, 22 developed postoperative ascites or AKI. In univariate analyses, a higher edema index and higher fluid infusion during surgery were significant risk factors for ascites or AKI in patients who underwent liver resection. Specifically, there was no significant difference between those with and without ascites or AKI with regard to the mean edema index values (0.385 *vs.* 0.381, P=0.056). However, the incidence of ascites or AKI was higher in patients with a high edema index (68.4% *vs.* 36.0%, P=0.033). In multivariate analysis, edema index >0.384 and higher fluid infusion during surgery were significant risk factors for postoperative ascites or AKI (*Table 3*). The AUC of the edema index was 0.645 (95% CI: 0.478–0.811; P=0.100) for predicting postoperative ascites or AKI.

Similarly, a subgroup analysis was performed on patients without cirrhosis (n=35, 44.3%). Among these, 13 developed postoperative ascites or AKI. In univariate analyses, a higher edema index, low phase angle, more extensive surgery, and larger HCC were significant risk factors for ascites or AKI in patients who underwent liver resection (*Table 4*). There was a significant difference in the mean edema index between those with and without ascites or AKI (0.390 *vs.* 0.382, P=0.001). There was a significant difference in the incidence of ascites or AKI (61.1% *vs.* 11.8%, P=0.003) between those with a high and low edema index. However, multivariate analysis showed that the edema index was not a significant predictor of postoperative ascites or AKI in patients without cirrhosis (OR 4.38; 95% CI: 0.35–55.38; P=0.254). The AUC of the edema index was 0.830 (95% CI: 0.696–0.965; P=0.001) for predicting postoperative ascites of AKI.

Predictive factors for postoperative survival in HCC patients

Four patients died during follow-up. Multivariate analysis showed that a large tumor size was the only predictive factor for poor survival after hepatectomy (hazard ratio 1.72, 95% CI: 1.05–2.83; P=0.033). Phase angle, sarcopenia, and edema index were not predictive of survival (*Table 5*, *Figure 2*).

Table 2 Risk factors for predicting postoperative ascites or AKI in all patients

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, ≥55 years	1.01 (0.41–2.48)	0.977		
Gender, male	2.31 (0.68–7.83)	0.178		
Liver cirrhosis	1.69 (0.68–4.18)	0.255		
Hemoglobin (g/dL)	0.80 (0.61–1.04)	0.100		
Platelet, >100 (10^3/μL)	0.84 (0.43–1.22)	0.084		
Creatinine, >1.2 mg/dL	0.62 (0.54–7.11)	0.699		
Albumin, <3.5 g/dL	–	0.999		
Bilirubin, >1.2 mg/dL	–	0.999		
INR	34.56 (0.13–9,319.63)	0.215		
ICGR15, >10%	0.56 (0.22–1.45)	0.234		
HCC size (cm)	1.09 (0.97–1.23)	0.151		
No. of resected segments	1.72 (1.10–2.67)	0.017	1.39 (0.85–2.28)	0.189
Edema index[a], >0.384	5.20 (1.99–13.64)	0.001	3.96 (1.03–15.17)	0.045
BMI (kg/m^2)	1.00 (0.87–1.14)	0.963		
Sarcopenia	1.01 (0.25–4.07)	0.993		
Phase angle, >5.5	0.36 (0.14–0.91)	0.030	0.75 (0.19–2.96)	0.681
Body cell mass (kg)	0.94 (0.86–1.02)	0.149		
Fluid infusion during operation (L)	1.38 (1.07–1.79)	0.015	1.36 (1.04–1.79)	0.026
Blood loss during operation (L)	1.16 (0.80–1.70)	0.438		
Transfusion during operation (L)	1.32 (0.88–2.00)	0.182		
Transfusion after operation (L)	1.91 (0.93–3.94)	0.078		

[a], edema index was calculated using extracellular water/total body water. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; INR, international normalized ratio; ICGR15 indocyanine green 15' retention test; HCC, hepatocellular carcinoma; BMI, body mass index.

Discussion

This prospective cohort study revealed that a high preoperative edema index (>0.384) was a significant predictive factor for postoperative ascites or AKI after hepatectomy in patients with HCC. The preoperative edema index was useful, especially for patients with cirrhosis. However, other indicators of BIA such as sarcopenia or phase angle did not predict postoperative complications or short-term survival after hepatectomy.

Previous studies have reported several predictive factors for ascites or AKI after hepatectomy. Advanced age, an increased Model for End-stage Liver Disease score, major hepatectomy, and prolonged surgery were reported as risk factors for AKI after liver surgery (10). Considering postoperative ascites, a study suggested that albumin <4.0 g/dL, platelet count <100×10^9/L, and operation time >250 min increased the incidence of ascites after hepatectomy (29). ICGR15 >10%, tumor size >10 cm, and red blood cell transfusion were also identified as risk factors for ascites after hepatectomy (7). In another study, a Child-Pugh score of 6 or 7 and major hepatic resection were reported to increase the incidence of post-hepatectomy ascites (30). In summary, the previously reported factors can be grouped into factors that reflect the severity of liver dysfunction and factors that reflect the extent of surgery. These factors have been overcome through careful patient selection, preoperative medical liver disease management,

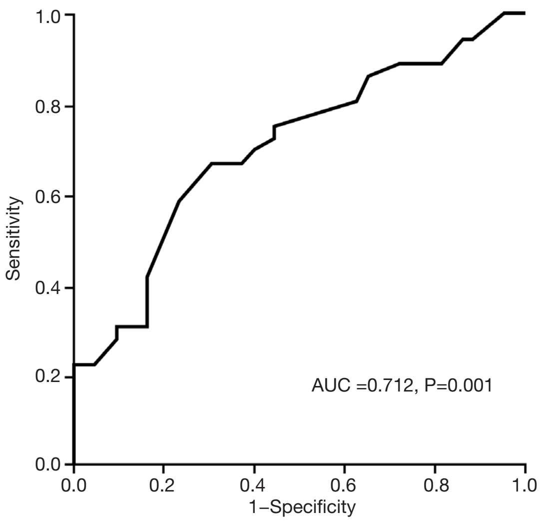

Figure 1 Receiver operating characteristic curve of the edema index for predicting postoperative ascites or acute kidney injury in all patients.

and advances in surgical techniques. As seen in the present study, most patients who underwent hepatectomy showed good baseline liver function. Therefore, it is necessary to provide an index that can further evaluate liver function in detail. Recently, liver stiffness measurements via transient elastography have been reported as predictive factors for ascites after hepatectomy (31,32). Liver stiffness measurement is a noninvasive method of evaluating hepatic venous pressure gradient and functional hepatic reserve by estimating hepatic fibrosis (31).

The present study suggests that the edema index obtained by BIA is a simple, easy, and clinically applicable method for volume status assessment of patients with liver disease. A previous study reported an increased edema index in patients with cirrhosis compared to that in healthy controls (25). The edema index also correlated with serum albumin and prothrombin time. Therefore, the edema index can be used to quantify body water redistribution.

Table 3 Risk factors for predicting postoperative ascites or AKI in patients with cirrhosis

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, ≥55 years	0.83 (0.26–2.72)	0.763		
Gender, male	1.86 (0.39–8.99)	0.439		
Hemoglobin (g/dL)	0.80 (0.54–1.18)	0.262		
Platelet, >100 (10^3/μL)	0.27 (0.05–1.50)	0.134		
Creatinine, >1.2 mg/dL	–	1.000		
Albumin, <3.5 g/dL	–	1.000		
Bilirubin, >1.2 mg/dL	–	1.000		
INR	65.16 (0.02–200,045.69)	0.308		
ICGR15, >10%	0.48 (0.12–1.94)	0.301		
HCC size (cm)	1.03 (0.82–1.30)	0.778		
No. of resected segments	1.16 (0.63–2.14)	0.641		
Edema index[a], >0.384	3.85 (1.09–13.66)	0.037	3.98 (1.05–15.07)	0.042
BMI (kg/m^2)	1.04 (0.87–1.23)	0.692		
Sarcopenia	1.58 (0.24–10.52)	0.637		
Phase angle, >5.5	0.48 (0.14–1.59)	0.230		
Body cell mass (kg)	0.94 (0.84–1.04)	0.218		
Fluid infusion during operation (L)	1.39 (1.00–1.93)	0.048	1.38 (1.00–1.91)	0.050
Blood loss during operation (L)	1.17 (0.74–1.85)	0.498		
Transfusion during operation (L)	1.43 (0.87–2.36)	0.157		
Transfusion after operation (L)	1.96 (0.78–4.96)	0.153		

[a], edema index was calculated using extracellular water/total body water. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; INR, international normalized ratio; ICGR15, indocyanine green 15' retention test; HCC, hepatocellular carcinoma; BMI, body mass index.

Table 4 Risk factors for predicting postoperative ascites or AKI in patients without cirrhosis

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, ≥55 years	1.56 (0.37–6.66)	0.550		
Gender, male	3.00 (0.43–20.95)	0.268		
Hemoglobin (g/dL)	0.77 (0.52–1.13)	0.180		
Platelet, >100 (10^3/μL)	–	1.000		
Creatinine, >1.2 mg/dL	1.75 (0.10–30.59)	0.701		
Albumin, <3.5 g/dL	–	1.000		
Bilirubin, >1.2 mg/dL	–	1.000		
INR	13.00 (0.01–35,428.40)	0.525		
ICGR15, >10%	0.49 (0.12–1.98)	0.316		
HCC size (cm)	1.185 (1.000–1.403)	0.050	1.10 (0.88–1.39)	0.394
No. of resected segments	3.11 (1.41–6.86)	0.005	2.28 (0.87–5.96)	0.093
Edema index[a], >0.384	4.267 (1.251–14.548)	0.020	4.38 (0.35–55.38)	0.254
BMI (kg/m^2)	0.86 (0.67–1.12)	0.262		
Sarcopenia	0.53 (0.05–5.68)	0.598		
Phase angle, >5.5	0.21 (0.04–0.97)	0.046	0.39 (0.03–4.66)	0.459
Body cell mass (kg)	0.92 (0.79–1.08)	0.295		
Fluid infusion during operation (L)	1.27 (0.77–2.09)	0.352		
Blood loss during operation (L)	0.95 (0.42–2.14)	0.909		
Transfusion during operation (L)	0.59 (0.16–2.16)	0.425		
Transfusion after operation (L)	1.68 (0.54–5.24)	0.371		

[a], edema index was calculated using extracellular water/total body water. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; INR, international normalized ratio; ICGR15, indocyanine green 15' retention test; HCC, hepatocellular carcinoma; BMI, body mass index.

According to Hara *et al.* (25), patients with edema index ≥0.398 demonstrated a higher risk of ascites than those with edema index <0.398. Our study demonstrated a difference in the incidence of ascites based on the median value of 0.384. The difference in cutoff value between our study and that of Hara *et al.* may be because of variations in study population and clinical setting. Their study considered ascites development only in patients with cirrhosis, whereas our study included both patients with and without cirrhosis. Furthermore, the previous study observed that the development of ascites was the natural course in cirrhosis without intervention. However, the current study observed the incidence of ascites after surgical intervention. These differences could have contributed to the lower edema index value for development of ascites in the current study.

BIA has recently become more common because of its convenience and efficacy, and it is widely used in liver disease. Ontanilla-Clavijo *et al.* reported that a significant correlation was found between peripheral impedance and hemodynamic change, and that impedance can be used for monitoring in patients with cirrhosis of the liver with refractory ascites (33). Studies using sarcopenia as a prognostic indicator in patients with liver cirrhosis (19), and studies predicting mortality as phase angle in patients with cirrhosis (20) and hepatobiliary cancer (21) have also been reported.

Gonzalez *et al.* reported that since standardization of BIA was lacking, caution was needed in interpreting results from BIA, considering that the prevalence of sarcopenia that has been reported covers a wide range among studies,

Table 5 Risk factors for predicting postoperative mortality after hepatectomy

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, ≥ 55 years	0.76 (0.11–5.43)	0.787	0.96 (0.07–13.60)	0.977
Gender, male	0.04 (0.00–1,545.79)	0.539	–	0.990
Liver cirrhosis	0.59 (0.08–4.22)	0.597		
Hemoglobin (g/dL)	2.52 (1.03–6.18)	0.043	4.14 (1.00–17.22)	0.050
Platelet, >100 (10^3/μL)	24.89 (0.00–8,692,674.86)	0.622		
Creatinine, >1.2 mg/dL	0.05 (0.00–91,580,381.97)	0.779		
Albumin, <3.5 g/dL	0.05 (0.00–5.5×10^{16})	0.886		
Bilirubin, >1.2 mg/dL	0.05 (0.00–222,721,769.7)	0.787		
INR	50.60 (0.00–9,833,458.33)	0.527		
ICGR15, >10%	0.11 (0.01–1.13)	0.063		
HCC size (cm)	1.29 (1.08–1.53)	0.005	1.72 (1.05–2.83)	0.033
No. of resected segments	2.25 (0.93–5.44)	0.073		
Edema index[a], >0.384	0.02 (0.00–57.40)	0.328		
BMI (kg/m^2)	0.82 (0.58–1.16)	0.263		
Sarcopenia	1.94 (0.20–18.87)	0.568		
Phase angle, >5.5	3.73 (0.39–36.04)	0.255		
Body cell mass (kg)	0.99 (0.83–1.18)	0.890		
Fluid infusion during operation (L)	1.07 (0.70–1.64)	0.740		
Blood loss during operation (L)	1.33 (0.84–2.10)	0.220		
Transfusion during operation (L)	0.81 (0.27–2.42)	0.710		
Transfusion after operation (L)	1.99 (0.93–4.24)	0.075		

[a], edema index was calculated using extracellular water/total body water. HR, hazard ratio; CI, confidence interval; INR, international normalized ratio; ICGR15, indocyanine green 15' retention test; HCC, hepatocellular carcinoma; BMI, body mass index.

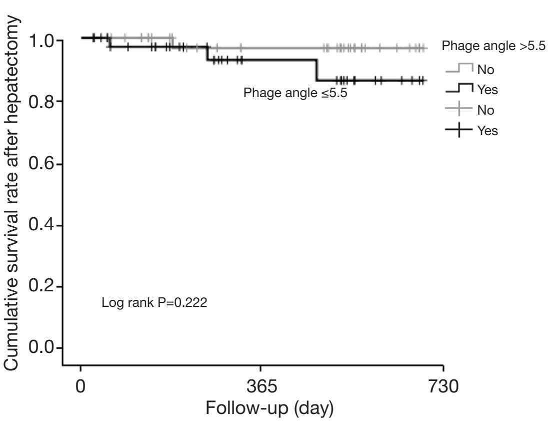

Figure 2 Patients survival rate after hepatectomy according to baseline phage angle.

even when conducted in the same population (34). However, BIA is a relatively accurate and convenient test compared to other tests in measuring the presence of sarcopenia (35). In addition, considering that the presence of sarcopenia can be applied as a prognostic factor in patients with liver cirrhosis (19) measuring the presence of sarcopenia using BIA has great clinical relevance.

However, in the present study, sarcopenia or phase angle was not significantly predictive of morbidity or mortality after hepatectomy. Considering the relatively short follow-up duration of our study (median 10.7 months), the role of BIA was not evident in predicting short-term survival after hepatectomy. The only significant factor for predicting short-term mortality was tumor burden. In fact, all four patients who died demonstrated HCC progression. Further studies showing whether sarcopenia or phase angle can predict long-term mortality are needed.

This study has a few limitations. Although the study was conducted on patients with early-stage operable HCC, we did not control for HCC stage in the study. Likewise, although the study included only patients with preserved liver function who underwent surgery, the study population had various etiologies. These factors could also have affected postoperative morbidity.

There is also a limitation that our study could not consider all other factors that could affect the edema index. Nevertheless, we thought the edema index may reflect underlying liver decompensation that may not be clearly identified with conventional tests.

In conclusion, the preoperative edema index can be used to predict the incidence of ascites or AKI after hepatectomy, particularly in patients with liver cirrhosis. BIA could provide additional clinical information regarding postoperative complications in patients with HCC scheduled for surgery.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Ajou University hospital (AJIRB-MED-OBS-16-287), and all patients provided informed consent.

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