Original Article

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Factors Associated with Perioperative Edema in Patients with Stage I Gastric Cancer Using a Body Composition Analyzer

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Summary: ***Purpose*:** Assessment of nutritional status and nutritional interventions is important in gastric cancer patients. We investigated the factors associated with perioperative edema in patients with stage I gastric cancer using a body composition analyzer.
***Methods*:** The study included 106 patients with stage I gastric cancer who underwent distal gastrectomy. The body composition of each patient was evaluated by bioelectrical impedance analysis (BIA) using an InBody 720 body composition analyzer. Patients with an extracellular water to total body water ratio of ≥ 0.4 before and 1 week after gastrectomy were considered to have edema, the cause of which was determined retrospectively.
***Results*:** Patients with preoperative edema were significantly older, had a significantly higher lymph node metastasis rate and disease stage, and had a significantly poorer Controlling Nutritional Status (CONUT) score, and Prognostic Nutritional Index (PNI) compared with patients without preoperative edema. The group with postoperative edema had significantly higher proportions of elderly and female patients as well as a higher rate of Billroth-II reconstruction compared with the group without postoperative edema. The group with postoperative edema also had significantly lower intracellular water content, total body water content, protein content, skeletal muscle mass, and PNI.
***Conclusions*:** Preoperative edema occurs in elderly patients with poor nutritional status, and postoperative edema occurs in elderly patients with a shorter operative time. Perioperative edema status assessed by BIA is thought to be related to perioperative nutritional status.

Keywords gastric cancer, bioelectrical impedance analysis, nutrition status, perioperative management, edema

INTRODUCTION

Postoperative malnutrition is common in patients who undergo gastrointestinal surgery. Although various methods are used to assess nutritional status, no gold standard has been established.

CONUT (Controlling Nutritional Status) has recently become known as a nutritional assessment tool and was presented at the ESPEN (European Society for Clinical Nutrition and Metabolism) Congress in 2003. In CONUT, scores are calculated for serum albumin level, total cholesterol level, and total lymphocyte count, and the sum of these three scores is used as a nutrition index. Therefore, the CONUT score reflects protein metabolism, lipid metabolism, and immune function. The severity of malnutrition is classified into

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Abbreviations: B-I, Billroth I; B-II, Billroth II; BIA, bioelectical impedance analysis; BMI, body mass index; CD, Clavien–Dindo; CI, confidence interval; CONUT, Controlling Nutritional Status; ECW/TBW, ratio of extracellular water to total body water; ERAS, Enhanced Recovery After Surgery; ESD, endoscopic submucosal dissection; ESPEN, European Society for Clinical Nutrition and Metabolism; NLR, neutrophil/lymphocyte ratio; PNI, Prognostic Nutritional Index; RY, Roux-en-Y; T-Chol, total cholesterol; TLC, total lymphocyte count.

4 levels: normal, mild, moderate, and severe [1].

Bioelectrical impedance analysis (BIA) has recently been attracting attention as a method for nutritional assessment. One index calculated by BIA, the ratio of extracellular water to total body water (ECW/TBW), is an edema index that shows the water balance between blood and interstitial fluid. Previous studies have shown ECW/TBW to be a particularly useful predictor of clinical outcomes in patients with chronic liver disease, renal impairment, heart failure, and other serious illnesses. This is because nutritional status is considered to be related to extracellular osmotic pressure [2,3].

However, few studies have examined how perioperative fluid balance is associated with surgery-related factors and nutrition in patients with gastric cancer.

In this study, we investigated the association between perioperative fluid balance and nutritional status after gastrectomy in patients with stage I gastric cancer, as outcomes are less impacted by tumor variables and chemotherapy at this stage.

MATERIALS AND METHODS

Participants and patient selection

This study was approved by the Institutional Review Board of Kurume University School of Medicine based on the Ethical Guidelines for Medical Research by the Ministry of Health, Labour and Welfare (approval number: 20098). All gastric cancer patients who underwent gastrectomy at Kurume University Hospital gave written consent for their specimens and test data to be used for research purposes.

Patients of the Department of Gastroenterological Surgery at Kurume University Hospital who met the following criteria between October 2016 and October 2020 were included in the study: (1) distal gastrectomy for gastric cancer; (2) body composition evaluated by BIA using a body composition analyzer (InBody720; InBody Japan, Inc., Tokyo, Japan) before and 1 week after gastrectomy; (3) the final diagnosis of stage IA or IB; (4) no residual gastric cancer. We excluded 1 patient on dialysis, 2 patients with chronic heart failure, and 1 patient with concurrent hepatocellular carcinoma from the study.

A total of 102 patients met the above criteria. Among these patients, 65 were male and 37 were female, and 90 had stage IA disease and 12 had stage IB disease. This study was a retrospective analysis of data from medical records.

Nutritional assessment

The Prognostic Nutritional Index (PNI), neutrophil/lymphocyte ratio (NLR), and CONUT score were used for nutritional assessment. Laboratory values used were white blood cell count, neutrophil count, lymphocyte count, and albumin level (g/dl) measured preoperatively, 1 week postoperatively, and 1 year postoperatively.

Total cholesterol (T-Chol) levels measured preoperatively and 1 year postoperatively were also used.

PNI was calculated as [(10 × Alb) + (0.005 × TLC)], (TLC: total lymphocyte count [/mm^3]). CONUT score was calculated as the sum of the Alb score, TLC score, and T-chol score, obtained from Alb (g/dL), TLC (/μL), and T-chol (mg/dL) measurements, respectively. The severity of malnutrition was determined as follows: 0-1 points, normal; 2-4 points, mild; 5-8 points, moderate; and >8 points, severe [1].

However, assessment at 1 year after gastrectomy was only performed in 53 patients.

Gastrectomy

Almost all patients underwent laparoscopic surgery: 2 patients underwent open surgery, 70 patients underwent laparoscopy, and 32 patients underwent robot-assisted surgery. The reconstruction technique used was Billroth I (B-I) in 76 patients, Roux-en-Y (RY) in 17 patients, and Billroth II (B-II) in 9 patients. Lymph node dissection was performed in all patients. The extent of dissection, as defined in the 2018 Japanese gastric cancer treatment guidelines (5th edition) [4], was D2 in 5 patients and D1+ in 97 patients.

Perioperative management and evaluations

All patients followed the Enhanced Recovery After Surgery (ERAS) program. Per this program, fluid intake was started on postoperative day 1, and oral intake was started on postoperative day 2.

The length of hospitalization was defined as the period from the date of surgery to the date of discharge. Postoperative complications were evaluated according to the Clavien–Dindo (CD) classification. and treatment was provided as necessary [5,6].

Evaluation of body composition

Body composition was evaluated by BIA using the InBody 720. The following parameters were measured: body mass index (BMI), intracellular water content, extracellular water content, total body water content, protein content, mineral content, body fat content, body weight, and skeletal muscle mass.

ECW/TBW

Based on the ratio of intracellular to extracellular water content of 62:38 in healthy individuals, the reference range for ECW/TBW was taken as 0.36 to 0.4. An ECW/TBW of ≥ 0.4 was considered to indicate edema; patients with a ratio of ≥ 0.4 were classified as having edema, and those with a ratio less than 0.4 were not considered to have edema [7,8]. Body composition factors, nutritional indices, surgical factors, clinicopathological factors, and CONUT score at 1 year after gastrectomy were compared between groups. The clinicopathological terms used in this paper conform to the 15th Edition of the Japanese Classification of Gastric Carcinoma (October 2017) [9].

Clinicopathological factors

Invasion depth (M/SM vs. MP), lymph node metastasis (N(+) vs. N(−)), stage (IA vs. IB), and histological type (differentiated vs. undifferentiated) were compared between groups.

Statistical analysis

JMP Pro 16.0.0 software (SAS Institute Inc.; Cary, NC) was used for statistical analysis. Parameters were compared between groups using the t-test for continuous variables and Fisher's exact test for categorical variables. Logistic regression analysis with "ECW/TBW ≥ 0.4 or < 0.4" as the dependent variable was used for analysis related to edema. Results with $P < 0.05$ were considered significant. Multivariate logistic regression was performed with parameters found to be significant in univariate logistic regression. However, due to the small number of events, the results of multivariate analysis are presented as supplemental results.

RESULTS

Characteristics of patients with and without preoperative/postoperative edema

The four groups were classified by preoperative

TABLE 1.
Characteristics of patient groups classified by preoperative and postoperative edema status

		Total (n=102)	Group A (n=10)	Group B (n=2)	Group C (n=8)	Group D (n=82)
Age, years Median (min-max)		70 (42-88)	82.5 (69-88)	73 (73)	75 (46-83)	68.5 (42-83)
Sex	Male/female	65/37	4/6	2/0	3/5	56/26
Surgical technique	Open/laparoscopic/robotic	2/68/32	0/10/0	1/1/0	0/5/3	1/52/29
Reconstruction technique	B1/RY/B2	76/17/9	6/0/4	1/0/1	6/1/1	63/16/3
Operative time, min Median (min-max)		261 (150-453)	216 (158-322)	405 (372-438)	255.5 (197-356)	266.5 (150-453)
Blood loss, g Median (min-max)		10 (1-8487)	14 (1-30)	4261 (35-8487)	10 (2-75)	10 (1-350)
Intraoperative fluid volume, mL Median (min-max)		2000 (600-4700)	1700 (900-2500)	4000 (3300-4700)	2250 (800-3500)	2000 (600-4100)
Length of postoperative hospitalization, days Median (min-max)		13 (9-65)	12.5 (11-50)	23 (12-34)	12 (12-22)	13 (9-65)
Stage	IA/ IB	90/12	7/3	1/1	7/1	75/7
Preoperative comorbidities (includes patients with multiple comorbidities)	Heart disease	8	2	0	1	5
	Lung disease	6	0	0	1	5
	Kidney disease	1	0	1	0	0
	Diabetes	21	3	1	1	16
	Liver disease (virus carrier)	5	0	0	0	5
	Steroids	1	0	0	1	1
Postoperative complications	CD1/CD2/CD3	3/14/6	1/0/1	0/0/1	0/2/0	2/12/4

B1, Billroth-I; RY, Roux-en-Y; B2, Billroth-II; CD, Clavien-Dindo
Group A: patients who had both preoperative and postoperative edema; Group B: patients who had preoperative edema but not postoperative edema; Group C: patients who had postoperative edema but not preoperative edema; Group D: patients who did not have preoperative or postoperative edema

TABLE 2.
Analyses related to edema

			Analyses using preoperative values of patients with preoperative edema (Groups A and B)				Analyses using postoperative values of patients with postoperative edema (Groups A and C)			
			Univariate logistic analysis		Multivariate logistic analysis		Univariate logistic analysis		Multivariate logistic analysis	
			OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95% CI)	P value
Age			1.299 (1.0911-1.384)	0.0007*	1.366 (1.106-1.687)	0.0038*	1.124 (1.024-1.214)	0.0026*	1.098 (0.99-1.217)	0.0756
Sex			0.525 (0.156-1.766)	0.2981			0.285 (0.099-0.819)	0.0197*	0.152 (0.007-3.334)	0.2318
Surgical factors	Reconstruction technique	B1 (ref)					1		1	
		B2					6.667 (1.56-28.483)	0.0105*	22.129 (1.381-354.718)	0.0284*
		RY					0.333 (0.04- 2.756)	0.308	0.215 (0.02-2.321)	0.2056
	Operative time						0.99 (0.981-0.999)	0.0383*	0.983 (0.969-0.996)	0.0134*
	Blood loss						0.992 (0.976-1.01)	0.3861		
	Intraoperative fluid volume						0.999 (0.999-1.0)	0.1173		
Preoperative comorbidities	Heart disease		2.372 (0.432-13.019)	0.3203			2.6 (0.585-11.56)	0.2094		
	Lung disease		not estimated				0.929 (0.102-8.473)	0.9482		
	Kidney disease		not estimated				not estimated			
	Diabetes		2.147 (0.579-7.967)	0.2534			1.126 (0.328-3.861)	0.8502		
	Liver disease		not estimated				not estimated			
	History of steroid therapy		not estimated				not estimated			
Clinicopathological factors	Invasion depth (M/SM vs. MP)		0.786 (0.086-7.149)	0.8304			1.308 (0.148-11.577)	0.8096		
	Lymph node metastasis (N1 vs. N0)		9.664 (1.694-55.127)	0.0107*	0.375 (0.016-8.836)	0.5425	5.4 (0.994-29.399)	0.0508		
	Histologic type (undifferentiated vs. differentiated)		0.436 (0.111-1.718)	0.2354			0.489 (0.16-1.494)	0.2091		
	Stage		5.126 (1.261-20.841)	0.0224*	8.516 (0.74-97.975)	0.0857	2.714 (0.719-10.25)	0.1408		
	Length of postoperative hospitalization						1.008 (0.954-1.066)	0.7707		
	Postoperative complications						0.94 (0.579-1.579)	0.801		

	Preoperative value					Postoperative value			
BIA parameters	Intracellular water content (L)	0.828 (0.684-1.001)	0.0515			0.813 (0.691-0.9571)	0.0127*	not estimated	
	Extracellular water content (L)	0.912 (0.685-1.214)	0.5292			0.861 (0.676-1.098)	0.2273		
	Total body water content (L)	0.929 (0.835-1.033)	0.1315			0.904 (0.82-0.997)	0.0423*	not estimated	
	Protein content (kg)	0.645 (0.416-1.002)	0.0509			0.622(0.428-0.906)	0.0133*	not estimated	
	Mineral content (kg)	0.374 (0.088-1.594)	0.1836			0.502 (0.158-1.594)	0.2422		
	Body fat mass (kg)	0.984 (0.895-1.082)	0.7406			1 (0.922-1.085)	0.9944		
	Body weight (kg)	0.964 (0.908-1.022)	0.2197			0.963 (0.915-1.013)	0.1467		
	Skeletal muscle mass (kg)	0.865 (0.747- 1.0)	0.0505			0.853 (0.753-0.967)	0.0127*	not estimated	
Blood biochemistry parameters	NLR	1.065 (0.766-1.479)	0.709			1.127 (0.883-1.438)	0.3375		
	PNI	0.822 (0.711-0.951)	0.0082*	1.137 (0.876-1.475)	0.3337	0.788 (0.683-0.909)	0.0011*	0.121 (0.749-1.68)	0.5785
	CONUT score (0-1 points vs. $\geq$2 points)	5.918 (1.805-19.408)	0.0033*	39.464 (2.548-611.431)	0.0086*				

*: Significant difference
BIA, bioelectrical impedance analysis; NLR, neutrophil/lymphocyte ratio; PNI, Prognostic Nutritional Index; CONUT, Controlling Nutritional Status

and postoperative edema status.

Ten patients had both preoperative and postoperative edema (Group A), 2 had preoperative edema but not postoperative edema (Group B), 8 had postoperative edema but not preoperative edema (Group C), and 82 did not have preoperative or postoperative edema (Group D) (Table 1).

Group A had large proportions of elderly and female patients. In this group, all patients underwent laparoscopic surgery, the operative time was shorter, the volume of intraoperative fluids given was lower than in the other groups, and the length of postoperative hospitalization was shorter. Four patients had preoperative comorbidities. One patient had a grade CD3 postoperative complication (10%).

In Group B, both of the 2 patients were male. One patient had postoperative pancreatic fistula (grade CD3) due to massive hemorrhage caused by intraoperative vascular injury, which resulted in conversion to open surgery. This patient therefore received large volumes of blood and albumin products intraoperatively and postoperatively. The other patient was undergoing additional surgery after endoscopic submucosal dissection (ESD). Preoperative comorbidities included renal disease in the patient with massive hemorrhage and diabetes mellitus in the patients undergoing additional surgery after ESD.

Group C had large proportions of elderly and female patients. Operative time was relatively short, stage IA was the most common stage, and the length of postoperative hospitalization was the shortest among all groups. Three patients had preoperative comorbidities. Two patients (25%) had a grade CD2 postoperative complication.

Group D was younger and had a larger proportion of men than the other groups. Twelve patients (4%) had a grade CD2 postoperative complication, and 4 (4%) had a grade CD3 postoperative complication.

Analysis of patients with preoperative edema

Table 2 (left side) shows the results for patients with preoperative edema (groups A and B).

The group with preoperative edema was significantly older, had a significantly higher rate of lymph node metastasis at a significantly higher stage (P = 0.0007, P = 0.0107, and P = 0.0224, respectively), and a significantly larger percentage of patients with a CONUT score of $\geq$ 2 (P = 0.0033) than the group without preoperative edema. They also had a significantly lower PNI (P = 0.0082).

Multivariate analysis showed older age and CONUT score to be independent factors for edema (P

= 0.0038 and P = 0.0086, respectively). This indicates that edema occurs in elderly patients with poor nutritional status.

Analysis of patients with postoperative edema

Table 2 (right side) shows the results for the analysis of patients with edema at 1 week after gastrectomy (groups A and C). The group with postoperative edema had significantly higher proportions of elderly and female patients, as well as a higher rate of Billroth-Ⅱ reconstruction compared with the group without postoperative edema (P = 0.0026, P = 0.0197, and P = 0.0105, respectively). The group with postoperative edema also had a significantly shorter operative time (P = 0.0383) and significantly lower intracellular water content, total body water content, protein content, skeletal muscle mass, and PNI (P = 0.0127, P= 0.0423, P = 0.0133, P = 0.0127, and P = 0.0011, respectively).

Multivariate analysis showed Billroth-Ⅱ reconstruction (P = 0.0284) and operative time (P = 0.0134) to be independent factors for edema.

These results suggested that edema occurred in patients with short surgical times who were selected for Billroth-Ⅱ reconstruction.

Nutritional status at 1 year after gastrectomy

An additional analysis was conducted to determine the effect of edema status before and after gastrectomy on nutritional status and immune function indicators at 1 year after gastrectomy (Supplementary Table 1). Because only a limited number of patients were followed for 1 year, the results are presented as supplemental results.

No patient had a CONUT score of ≥ 5. Patients with preoperative edema had significantly higher NLR at 1 year after gastrectomy (P = 0.035). Patients with postoperative edema had significantly T-cho and PNI (P = 0.023, and P = 0.014, respectively) and significantly higher NLR ($P < 0.001$) at 1 year after gastrectomy. In addition, the proportion of patients with a CONUT score of ≥ 2 at 1 year after gastrectomy was significantly higher in patients with postoperative edema (P = 0.007). This indicates that edema at 1 week after gastrectomy was associated with poor nutritional status at 1 year after gastrectomy.

DISCUSSION

Body composition has been shown to correlate with nutritional status and clinical outcomes because it can be used as a measure of body fat and muscle mass [10,11]. We measured the body composition of gastric cancer patients before and after gastrectomy to determine its utility in this population. The main parameter we focused on was ECW/TBW obtained from BIA.

ECW/TBW is considered a suitable prognostic factor for patients who are critically ill or have a highly invasive disease. Studies have shown that lower ECW/TBW is associated with lower rehospitalization and mortality rates in patients hospitalized with acute heart failure and that higher ECW/TBW is associated with poorer nutritional status and a worse prognosis in critically ill patients [12,13].

In a state of malnutrition, loss of intracellular and cellular components results in an increase in extracellular components, leading to edema [14,15]. This is why the edema indicator ECW/TBW may also be useful in nutritional assessment. Previous studies have shown that ECW/TBW is 0.38 in healthy individuals of all races, and ≥ 0.4 in people with edema [7,8,16,17]. To summarize the results of our study, the group of patients with preoperative edema (ECW/TBW ≥ 0.4) had a significantly higher proportion of patients with high CONUT scores, suggesting poor nutritional status before surgery. The reason why the group with both preoperative and postoperative edema developed edema after gastrectomy despite having a shorter operative time and receiving a lower volume of intraoperative fluids is likely related to the large proportion of elderly patients in that group. This highlights the need for careful preoperative management of elderly patients with preoperative edema.

The group with postoperative edema (ECW/TBW ≥ 0.4) most often underwent B-Ⅱ reconstruction. In our department, we often select the B-Ⅱ technique for patients with a small remnant stomach who are elderly or have poor performance status (PS) and the RY method for patients with good nutritional status. Elderly people were more likely to undergo resection surgery and B-Ⅱ reconstruction, and as a result, the surgery time was shorter.

Consequently, a likely reason why operative time was significantly longer in patients without edema in this study is because RY reconstruction is more complicated and takes longer than B-Ⅱ reconstruction.

Reduced skeletal muscle mass appeared to be a factor in postoperative edema. Low skeletal muscle mass has been shown to affect postoperative complications and prognosis [18-20] and is also associated with sarcopenia [21]. Sarcopenia is determined by muscle mass, muscle strength, and physical function. The causes include age-related changes, malnutrition, and inactivity [22,23]. Low skeletal muscle mass is observed in 85% of all patients with gastric cancer, and one cause of low muscle mass is malnutrition [24]. This is because nausea and mechanical obstruction after gastrectomy can lead to decreased food intake and particularly, inadequate protein intake [21,25]. Therefore, patients with gastric cancer are considered to be at high risk for sarcopenia.

Both skeletal muscle mass and PNI were significantly lower in patients with edema than in those without edema, in both the preoperative and postoperative phases. Both skeletal muscle mass and PNI were lower in elderly patients. Therefore, we speculated that age was as an independent factor associated with both preoperative and postoperative edema [25].

We also found that postoperative weight was lower (although not significantly) than preoperative weight, suggesting that surgical invasiveness and postoperative nutritional status may be related.

In patients undergoing surgery for esophageal cancer, ECW/TBW should return to baseline by postoperative days 6 or 7, regardless of complications or postoperative inflammation [26]. In this study, we evaluated ECW/TBW on postoperative day 7, and our results suggest that nutritional supplementation may not be feasible in patients whose ECW/TBW does not improve by that point.

ECW/TBW is considered a predictor of response durability in advanced lung cancer because patients with high ECW/TBW receiving pharmacotherapy tend to discontinue treatment within 1 year [27]. Because factors such as surgical technique, stage, and adjuvant therapy affect postoperative nutritional intake, we decided to include only patients with stage I disease (which is not treated with chemotherapy) in this study to minimize those effects.

In this study, patients with preoperative edema had a higher NLR and poorer nutrition and immune function at 1 year after gastrectomy, and patients with postoperative edema had significantly worse nutrition and immune function at 1 year after gastrectomy. Our results indicate that ECW/TBW at 1 week after gastrectomy is especially useful for determining whether a patient with stage I gastric cancer is at high risk for malnutrition.

Our study has a few biases. First, it is a retrospective single-center study. Second, the sample size is small. Third, inadequate cardiac and renal function may affect ECW/TBW as an edema indicator.

In conclusion, a large proportion of patients with stage I gastric cancer who develop edema in the perioperative period are elderly and have low skeletal muscle mass. Because the muscle mass and strength of elderly people with sarcopenia are improved by nutritional supplementation, these patients should be targeted for nutritional intervention, including oral nutritional supplements, and a nutrition support team should be involved in their care [28].

CONCLUSION

Preoperative edema occurs in elderly patients with poor nutritional status, and postoperative edema occurs in elderly patients with a shorter operative time. Perioperative edema status assessed by BIA is thought to be related to perioperative nutritional status. Although this study investigated a small number of cases, the results suggested that perioperative edema status may be related to nutritional status after 1 year.

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Supplementary TABLE 1.
Comparison of blood biochemical parameters at 1 year after gastrectomy

		Group without preoperative edema n=50	Group with preoperative edema n=3	P value	Group without postoperative edema n=46	Group with postoperative edema n=7	P value
	Cholesterol	187 (131-259)	172 (139-200)	0.116	188.0 (131.0-259.0)	171.5 (139.0-211.0)	0.023*
	NLR	1.45 (0.67-4.85)	2.16 (2.05-4.33)	0.035*	1.37 (0.67-3.82)	2.65 (0.90-4.85)	<0.001*
	PNI	51.39 (38.34-60.18)	51.32 (41.53-52.22)	0.254	51.53 (38.34-60.18)	48.39 (41.53-52.79)	0.014*
CONUT	0-1 points	39	1	0.145	38	2	0.007*
	≥2 points	11	2		8	5	

*: Significant difference
Data are shown as the median (25%CI-75%CI)
CI, confidence interval; NLR, neutrophil/lymphocyte ratio; PNI, Prognostic Nutritional Index; CONUT, Controlling Nutritional Status