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ORIGINAL ARTICLE

Extracellular water to total body water ratio, a novel predictor of recurrence in patients with colorectal cancer

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Abstract

Background: Total body water (TBW) fraction, which accounts for 60% of body weight, is an important indicator of body composition, and the extracellular water to TBW ratio (ECW/TBW) is reportedly useful in predicting clinical outcomes of patients with organ disorders. We aimed to clarify the clinical impact of preoperative ECW/TBW status on survival outcomes in cancer patients.

Methods: We used a database of 320 colorectal cancer (CRC) patients who underwent potentially curative resections. Preoperative ECW/TBW was measured using a bioelectrical impedance analysis (BIA), and its correlation with patient survival outcomes, clinicopathological factors, laboratory data, and comorbidities were analyzed.

Results: A high preoperative ECW/TBW was significantly associated with poorer relapse-free survival (RFS; $p=0.001$) and overall survival (OS; $p=0.003$). A high ECW/TBW ratio was significantly associated with older age ($p<0.001$), low BMI ($p=0.009$), and right-sided tumors ($p=0.03$). In a multivariate analysis, a high ECW/TBW significantly predicted a higher RFS mortality (HR: 2.07, 95% CI: 1.10–3.88, $p=0.024$) and OS mortality (HR: 3.23, 95% CI: 1.25–8.36, $p=0.016$). Furthermore, a high ECW/TBW was significantly associated with lower hemoglobin ($p<0.001$) and albumin levels ($p<0.001$), but not comorbidities.

Conclusions: A high preoperative ECW/TBW was a predictive factor for recurrence and poorer overall survival independent of the tumor, node, and metastasis (TNM) stage. Our data suggest that preoperative evaluation of ECW/TBW using BIA might serve as a novel tool for developing CRC treatment strategies.

KEYWORDS
colorectal cancer, extracellular water, intracellular water, prognosis, recurrence

1 | INTRODUCTION

Bioelectrical impedance analysis (BIA) is a simple and noninvasive tool for objectively calculating body compositions, such as fat, protein, minerals, and body water.[1] Body composition assessment in patients with various diseases is essential because unfavorable changes in body composition could be responsible for low exercise capacity, sarcopenia, cachexia, and frailty, which lead to poor patient outcomes.[1,2] In cancer patients, BIA assessment for sarcopenia or obesity is reportedly useful for predicting poor patient outcomes.[3,4] Of the body composition parameters, the total body water (TBW) fraction is an important indicator that accounts for 60% of the body weight. Cancer and extracellular water (ECW) are closely linked, as cancer generally elevates the metabolic rate and induces malnutrition, inflammation, and fluid retention conditions, including ascites, pleural effusion, and edema of peripheral extremities.[5] In addition, the ECW to TBW ratio (ECW/TBW) shows a significant association with patient body composition statuses, such as cachexia, sarcopenia, and frailty.[6]

ECW/TBW is generally used as an indicator of volume overload in clinical practice. Recent reports have shown that ECW/TBW is useful in predicting clinical outcomes of patients with organ disorders, such as heart failure,[7] renal dysfunction,[8] and hepatic dysfunction.[9] In addition, a high ECW content has been reported to predict significantly poorer prognoses in metastatic cancer patients, even in those receiving palliative care.[10] Recent reports have also shown that the viscosity and macromolecular composition of ECW impacts biological responses, including cell migration and morphological changes in cancer cells.[11] However, there have been no studies that have assessed the clinical impact of the preoperative ECW/TBW in cancer patients after a curative resection. Given the association of the ECW/TBW with cancer patients' outcomes, it is of clinical interest to clarify whether preoperative ECW/TBW has a significant association with recurrence.

Therefore, we hypothesized that cancer patients with a high ECW/TBW would have more recurrences and poorer outcomes. We used a database of 320 colorectal cancer (CRC) patients that underwent potentially curative resections and retrospectively examined the effectiveness of preoperative ECW/TBW as a predictive index for patient outcomes.

2 | METHODS

2.1 | Patients

We enrolled 1013 consecutive CRC patients who underwent elective primary tumor resections at Kumamoto University Hospital (Kumamoto, Japan) between April 2005 and June 2019. As shown in Figure 1A, the patients without preoperative ECW/TBW data and those with Stage IV CRC were excluded. Finally, 320 CRC patients who underwent potentially curative resections with preoperative ECW/TBW data were enrolled in this study. There were 198 male and 122 female patients with a median age of 68 years (19–90 years). Patients were followed-up in our hospital or affiliated hospitals until March 31, 2020, or death, whichever came first. Our surgical procedures were based on the Japanese CRC treatment guidelines,[12] and tumor staging was based on the 8th edition of the Union for International Cancer Control classification.[13] The protocol of this study was approved by the human ethics review committee of the Graduate School of Medicine, Kumamoto University (Institutional Review Board number 1047), and carried out according to the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.2 | Bioelectrical impedance analysis (BIA) for the calculation of ECW/TBW

Preoperative ECW/TBW was assessed by our clinical staff on the date of admission for surgery using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace, Tokyo, Japan). ECW and TBW content were calculated based on sex, height, obtained resistance value, and reactance value. A classification and regression tree (CART) analysis for the recurrence-free survival (RFS) was performed to determine the cut-off value of ECW/TBW (Figure S1). The cut-off value was 0.389, and we defined an ECW/TBW greater than 0.389 as a high ECW/TBW and less than or equal to 0.389 as a low ECW/TBW.

2.3 | Clinicopathological factors and preoperative laboratory data

Patient clinical records were reviewed to collect baseline data regarding sex; age; body mass index (BMI); tumor location; depth of tumor invasion; lymph node metastasis; tumor, node, and metastasis (TNM) stage; and comorbidities, including cardiac disease, respiratory disease, liver disease, renal dysfunction, and hyperlipidemia. The complications were classified as severe if they had a Clavien–Dindo classification greater than or equal to III. Laboratory data were collected within 2 weeks of surgery, including carcinoembryonic antigen (CEA; ng/mL), carbohydrate antigen 19-9 (CA19-9: U/mL), total neutrophil count (/mm^3), total lymphocyte count (/mm^3), hemoglobin (g/dL), platelet (/μL), albumin (g/L), total cholesterol (mg/dL), and C-reactive protein (CRP; mg/L). The positivity of CEA (>5.0 ng/mL) and CA19-9 (> 37 U/mL) was defined based on past reports.[14,15]

2.4 | Statistical analysis

We performed all statistical analyses using R V.3.4.4 (R Development Core Team) or JMP version 16 (SAS Institute Inc., Cary, NC, USA). Overall survival (OS) was defined as the interval from the date of resection to the date of death from any cause, while RFS was defined as the interval from the date of resection to the first date of confirmed recurrence or death. We used spline plots to evaluate the hazard ratio (HR) of relapse as a continuous function of ECW/TBW and a CART analysis to determine the ECW/TBW and the skeletal muscle mass index (SMI)

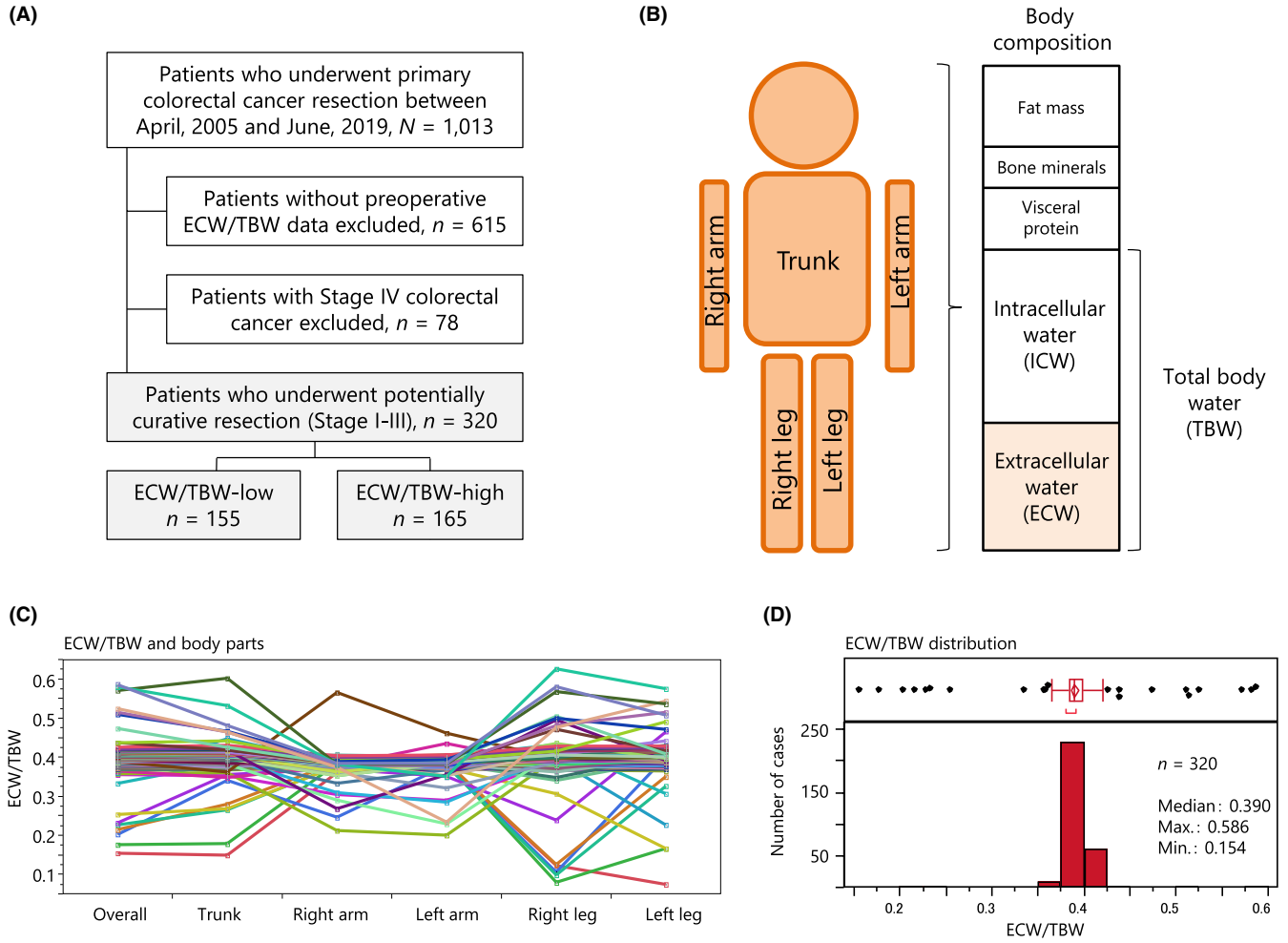

FIGURE 1 (A) Flow chart showing the data collection for this study (inclusion/exclusion criteria). (B) Calculation of ECW/TBW using InBody 720. (C) Variation of ECW/TBW in each body part. (D) The median value of ECW/TBW was 0.390 (range: 0.154–0.586).

cut-off value using RFS probability as endpoints.[16] The Kaplan–Meier method and log-rank test were used for the survival analysis. The chi-square test (case number ≥5) and Student's *t*-test were used for categorical and continuous variables, respectively. The multivariate Cox proportional hazards analysis (using the maximum likelihood model) was adjusted for sex, age, BMI, tumor location, depth of tumor invasion, lymph node metastasis, postoperative complication, and ECW/TBW to calculate HRs and 95% confidence intervals (CIs). We defined a *p*-value less than 0.05 as significant in all the analyses.

3 | RESULTS

3.1 | ECW/TBW in patients with colorectal cancer

We enrolled a total of 320 CRC patients who underwent potentially curative resections with preoperative ECW/TBW data in this study (Figure 1A). ECW/TBW was separately calculated for each body part, such as the trunk, right arm, left arm, right leg, and left leg, using InBody 720 (Figure 1B). Since the value of ECW/TBW varied in the body parts of each patient (Figure 1C), we decided to use the whole-body ECW/TBW for the analysis. The median ECW/TBW value was 0.390 (0.154–0.586; Figure 1D).

3.2 | ECW/TBW and patient survival outcome

First, the association between preoperative ECW/TBW and patient survival was analyzed. We used a spline plot, which showed the HRs for relapse, to show the clinical significance of ECW/TBW (Figure S1). ECW/TBW was prognostic for RFS, where the risks gradually increased as the ECW/TBW increased. Our CART analysis showed that 0.389 was the optimal cut-off value for RFS, and we separated the cases into two populations: those with a high ECW/TBW ($n=165$) and a low ECW/TBW ($n=155$) (Figure S1). Patients with a high ECW/TBW had significantly poorer RFS and OS than those with a low ECW/TBW. In the patients with a high ECW/TBW and low ECW/TBW, the 5-year RFS rates were 72.9 and 86.0% ($p=0.001$), respectively (Figure 2A), while the 5-year OS rates were 82.5 and 94.6% ($p=0.003$), respectively (Figure 2B). Moreover, in the patients with a high ECW/TBW and low ECW/TBW, recurrence rates were 13.4 and 8.4% ($p=0.154$), and the 5-year cancer-specific

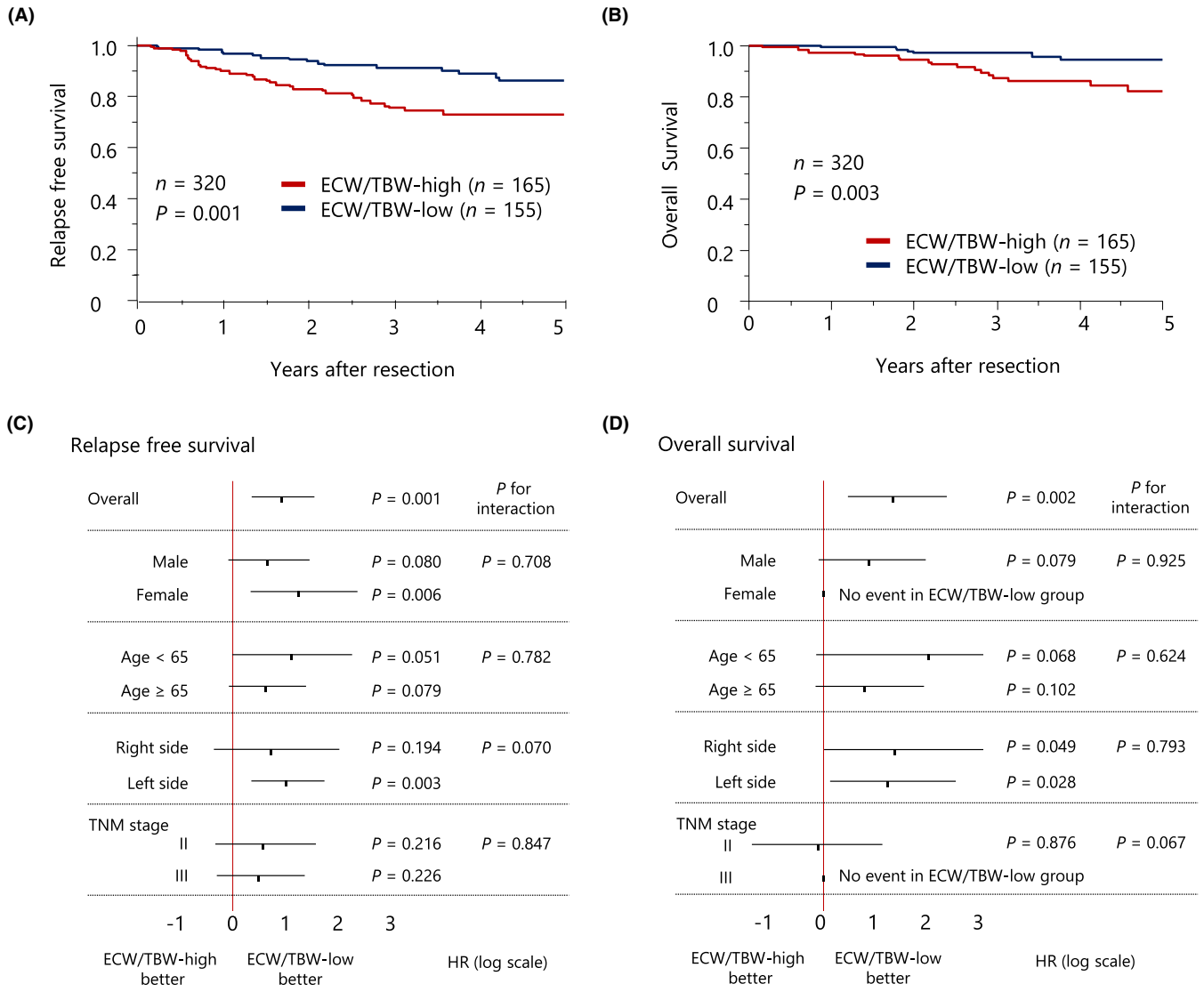

FIGURE 2 (A, B) The probabilities for the relapse-free survival and the overall survival according to ECW/TBW. (C, D) Subgroup analysis according to clinicopathological factors to assess the survival benefit of a low ECW/TBW.

survival rates were 88.4 and 97.4% ($p=0.007$), respectively. In the subgroup analysis, regarding the RFS, female patients ($p=0.006$, $p_{\text{for interaction}}=0.708$) and patients with a left-sided tumor ($p=0.003$, $p_{\text{for interaction}}=0.070$) and with a low ECW/TBW had a risk–benefit. However, there was no risk–benefit according to the TNM stage and low ECW/TBW (Figure 2C). Regarding the OS, patients with a right-sided tumor, and those with a left-sided tumor coinciding with a low ECW/TBW had a risk–benefit ($p=0.049$ and $p=0.028$, $p_{\text{for interaction}}=0.793$). There was no risk–benefit in female patients with a low ECW/TBW and patients with a TNM stage III (Figure 2D).

3.3 | ECW/TBW and clinicopathological factors

We next evaluated the association between preoperative ECW/TBW and clinicopathological factors (Table 1). A high ECW/TBW was significantly associated with older age ($p<0.001$), low BMI ($p=0.009$), right-sided tumors ($p=0.030$), and high CEA levels ($p=0.037$). There was no significant association between ECW/TBW and sex, depth of tumor invasion, lymph node metastasis, TNM stage, the status of preoperative chemotherapy, and the status of adjuvant chemotherapy. We also evaluated the association between preoperative ECW/TBW and other inflammation and nutritional markers: Glasgow prognostic scale (GPS), prognostic nutritional index (PNI) and Controlling Nutritional Status (CONUT). We set cut-offs of those markers based on previous studies. All of those markers were significantly associated with preoperative ECW/TBW status ($p=0.002$, 0.001, 0.016, respectively; Table S1).

3.4 | Independent clinical impact of ECW/TBW on the survival outcome

We also examined the independent clinical impact of preoperative ECW/TBW on the survival outcome. In multivariate analysis (Table 2),

TABLE 1 Association between ECW/TBW and clinicopathological factors.

Factors	Overall $n=320$ n (%)	ECW/TBW-low $n=155$ n (%)	ECW/TBW-high $n=165$ n (%)	p value[a]
Sex				
Male	198 (62%)	103 (66%)	95 (58%)	0.102
Female	122 (38%)	52 (34%)	70 (42%)	
Age				
<65	115 (36%)	81 (52%)	34 (21%)	<0.001
≥65	205 (64%)	74 (48%)	131 (79%)	
BMI				
<18.5	31 (10%)	8 (5%)	23 (14%)	0.009
18.5≤, <25	215 (67%)	104 (67%)	111 (67%)	
≥25	74 (23%)	43 (28%)	31 (19%)	
Tumor location				
Right side	88 (27%)	34 (22%)	54 (33%)	0.030
Left side	232 (73%)	121 (78%)	111 (67%)	
Depth of tumor invasion				
T1	80 (25%)	44 (28%)	36 (22%)	0.329
T2	58 (18%)	31 (20%)	37 (16%)	
T3	137 (43%)	60 (39%)	77 (47%)	
T4	45 (14%)	20 (13%)	25 (15%)	
Lymph node metastasis				
Negative	226 (71%)	114 (74%)	112 (68%)	0.265
Positive	94 (29%)	41 (26%)	53 (32%)	
Stage				
I	114 (36%)	62 (40%)	52 (32%)	0.260
II	114 (36%)	53 (34%)	61 (36%)	
III	92 (28%)	40 (26%)	52 (32%)	
CEA (ng/mL)				
≤5	224 (70%)	117 (75%)	107 (65%)	0.037
>5	96 (30%)	38 (25%)	58 (35%)	
CA19-9 (U/mL)				
≤37	271 (85%)	136 (88%)	135 (82%)	0.140
>37	49 (15%)	19 (12%)	30 (18%)	
Preoperative chemotherapy				
Presence	13 (4%)	6 (4%)	7 (4%)	0.720
Absence	307 (96%)	149 (95%)	158 (96%)	
Adjuvant chemotherapy				
Single-Agent	32 (10%)	16 (10%)	16 (10%)	0.946
Double-Agent	50 (16%)	25 (16%)	25 (15%)	
Absence	238 (74%)	114 (74%)	124 (75%)	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECW, extracellular water; TBW, total body water.

[a]p value was based on chi-square test for categorical factors.

a high ECW/TBW was an independent predictor of a higher RFS mortality (HR: 2.07, 95% CI: 1.10–3.88, $p=0.024$), as was deeper tumor invasion (HR: 2.05, 95% CI: 1.06–3.96, $p=0.032$) and positive lymph node metastasis (HR: 2.77, 95% CI: 1.33–5.76, $p=0.006$). Similarly, a high ECW/TBW was an independent predictor of higher OS mortality (HR: 3.23, 95% CI: 1.25–8.36, $p=0.016$). Moreover, we compared efficacy as a prognostic factor between ECW/TBW and other markers reflecting nutrition and inflammation. As shown in Table S2, ECW/TBW was a superior prognosticator for patients' survival compared with other markers. We also compared the ECW/TBW status and SMI, skeletal muscle mass/height (m)/height (m), as a marker of body composition. CART analysis showed that 7.404 was the optimal cut-off value of SMI for RFS (Figure S2). Univariate and multivariate analysis revealed that SMI was an independent prognostic marker of OS and RFS along with ECW/TBW (Table S2).

3.5 | The association of ECW/TBW with laboratory data and comorbidities

Finally, we examined the association of preoperative ECW/TBW with laboratory data and comorbidities. Table 3 shows that a high ECW/TBW was significantly associated with lower hemoglobin ($p<0.001$) and albumin levels ($p<0.001$). However, there was no significant correlation between ECW/TBW and preoperative comorbidities (Table S3).

4 | DISCUSSION

We hypothesized that CRC patients with a high ECW/TBW would have more recurrences and poorer outcomes even after curative resection. Using a database of 320 CRC cases, our study showed that a high preoperative ECW/TBW was a predictive factor for recurrence and poor OS independent of the TNM stage. In addition, a high ECW/TBW was significantly associated with older age, lower BMI, right-sided tumors, and lower albumin and hemoglobin levels, but not with TNM stage or comorbidities.

This is the first study, to our knowledge, demonstrating the effectiveness of ECW/TBW as a predictive factor for recurrence in cancer patients. Recent research has shown the predictive nature of cachexia, leading to sarcopenia and frailty, for postoperative recurrence in cancer patients.[2-4] Since sarcopenic patients, evaluated by muscle mass, have poorer tolerance to cancer therapies with a greater incidence of complications, chemotherapy toxicity, and perioperative problems, including recurrence, the evaluation of sarcopenic status can help to develop treatment strategies. In addition, accumulating evidence has shown that sarcopenia and frailty can be induced by various mechanisms, such as malnutrition, systemic inflammation, and other organ diseases. Previous studies have indicated that a high ECW/TBW was related to the volume of cancer[17] and poorer tolerance to cancer therapies[18] and induced postoperative complications in esophageal,[19] head and neck,[20] and lung cancers.[21] Moreover, poor prognoses in patients with metastatic cancers are known.[10] Furthermore, several reports have indicated that ECW/TBW, compared with other BIA parameters, such as muscle and fat mass, more accurately detects frailty,[3,21,22] which

TABLE 2 Association between ECW/TBW status and patient survival outcome.

Clinicopathological factors	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)[a]	*p* value
Relapse free survival				
Sex				
Male/Female	0.71 (0.41–1.22)	0.208	0.95 (0.54–1.67)	0.858
Age				
≥65/ <65	2.09 (1.15–4.07)	0.015	1.69 (0.85–3.35)	0.131
BMI				
<18.5/18.5≤, <25	1.32 (0.50–2.92)	0.547	0.70 (0.27–1.80)	0.463
≥25/18.5≤, <25	1.03 (0.52–1.91)	0.923	1.42 (0.73–2.73)	0.298
Tumor location				
Right side/Left side	1.10 (0.58–1.95)	0.763	0.95 (0.50–1.83)	0.885
Depth of tumor invasion				
T3–T4/T1–T2	2.69 (1.48–5.24)	<0.001	2.05 (1.06–3.96)	0.032
Lymph node metastasis				
Positive/Negative	2.88 (1.68–4.97)	<0.001	2.77 (1.33–5.76)	0.006
Postoperative complication				
CD classification ≥III/ <III	1.89 (0.95–3.49)	0.070	1.85 (0.91–3.77)	0.090
Preoperative chemotherapy				
Presence/Absence	0.40 (0.06–2.91)	0.367	0.33 (0.04–2.44)	0.277
Adjuvant chemotherapy				
Presence/Absence	1.70 (0.96–2.93)	0.069	0.84 (0.39–1.81)	0.650
ECW/TBW				
High/Low	2.52 (1.43–4.67)	0.001	2.07 (1.10–3.88)	0.024
Overall survival				
Sex				
Male/Female	1.22 (0.57–2.84)	0.621	1.97 (0.83–4.66)	0.122
Age				
≥65/<65	3.94 (1.51–13.48)	0.004	2.73 (0.90–8.27)	0.075
BMI				
<18.5/18.5≤, <25	1.52 (0.35–4.61)	0.530	0.78 (0.21–2.95)	0.714
≥25/18.5≤, <25	1.53 (0.64–3.44)	0.325	1.98 (0.82–4.76)	0.128
Tumor location				
Right side/Left side	2.40 (1.10–5.15)	0.029	2.03 (0.89–4.61)	0.093
Depth of tumor invasion				
T3–T4/T1–T2	1.48 (0.69–3.37)	0.315	1.42 (0.61–3.27)	0.415
Lymph node metastasis				
Positive/Negative	1.35 (0.58–2.94)	0.468	1.64 (0.55–4.87)	0.373
Postoperative complication				
CD classification ≥III/<III	1.08 (0.32–2.82)	0.890	1.39 (0.45–4.32)	0.566
Preoperative chemotherapy				
Presence/Absence	–	0.999	–	0.999
Adjuvant chemotherapy				
Presence/Absence	1.04 (0.43–2.30)	0.924	0.67 (0.21–2.14)	0.502
ECW/TBW				
High/Low	3.70 (1.58–10.13)	0.002	3.23 (1.25–8.36)	0.016

Abbreviations: CD classification, Clavien–Dindo classification; CI, confidence interval; ECW, extracellular water; HR, hazard ratio; TBW, total body water.

[a]Multivariate Cox proportional hazards regression model was adjusted for sex, age, tumor location, depth of tumor invasion, lymph node metastasis, postoperative complication and ECW/TBW status.

TABLE 3 Association between ECW/TBW status and preoperative serum data.

Preoperative serum data	Overall $n=320$	ECW/TBW-low $n=155$	ECW/TBW-high $n=165$	
	Mean ± SD	Mean ± SD	Mean ± SD	p value[a]
Neutrophil (/mm^3)	3538.5 ± 1604.2	3522.0 ± 1570.9	3553.9 ± 1639.5	0.859
TLC (/mm^3)	1644.7 ± 849.4	1698.0 ± 524.7	1594.6 ± 1067.5	0.277
Hb (g/dL)	12.4 ± 1.9	13.1 ± 1.7	11.7 ± 1.8	<0.001
Platelet ×10^3 (/μL)	232.5 ± 76.2	240.2 ± 68.0	225.3 ± 82.8	0.079
Albumin (g/L)	38.0 ± 4.7	39.2 ± 4.3	36.8 ± 4.7	<0.001
Total cholesterol (mg/dL)	188.3 ± 41.3	191.1 ± 40.2	185.6 ± 42.1	0.237
CRP (mg/L)	4.4 ± 10.8	3.1 ± 8.1	5.5 ± 12.7	0.051

Abbreviations: ECW, extracellular water; SD, standard deviation; TBW, total body water.

[a]p value was based on Student's t-test for continuous factors.

suggests that a high ECW/TBW might subsequently cause cachexia leading to sarcopenia and frailty in cancer patients.[22] Recently, Katsura et al. analyzed 114 cachexia cancer patients and concluded that ECW/TBW might be associated with mortality.[23] Since the ECW/TBW measurement can assess potentially unfavorable conditions for cancer treatments, ECW/TBW might predict recurrence in CRC patients after curative resection.

Our findings demonstrated that a high ECW/TBW was strongly associated with lower albumin and hemoglobin levels. These results are consistent with past reports, which imply that fluid imbalance is closely associated with malnutrition and systemic inflammation.[6] Since the fluid balance between the intracellular and extracellular space is based on fluid volume and pressure, hypoalbuminemia, which is crucial to maintaining colloidal osmotic pressure, can lead to a high ECW/TBW. Furthermore, cytokines generated by cancer cells cause systemic inflammation, and systemic inflammation markers, such as CRP[22] and interleukin-6,[24] are reportedly associated with hypervolemic statuses, suggesting an association between high CRP levels and high ECW/TBW. Previous reports have also clarified that anemia was significantly related to malnutrition and systemic inflammation.[25,26] Tumors may bleed and cause abnormal malnutrition and systemic inflammation, leading to iron, folate, and vitamin B12 deficiencies, all of which cause anemia. In other words, any condition that induces malnutrition, systemic inflammation, and anemia could lead to a high ECW/TBW status. Interestingly, the nutrition and systemic inflammation statuses are reported to affect the immune status, which could lead to tumor recurrence.[27,28] In addition, anemia might cause hypoxia in the tumor microenvironment, leading to T-cell apoptosis and activation of tumor-associated macrophages, inhibiting effector functions of tumor-infiltrating lymphocytes. This mechanism can induce poor immune function. Considering these pieces of evidence, it may be plausible that a high preoperative ECW/TBW, which is more frequent in patients with lower nutrition, higher systemic inflammation, and anemia, could predict poor immune function. However, other recent reports have indicated that chronic inflammation may cause hyperosmotic stress and play an important role in carcinogenesis.[29] Further research is needed to show the possibility that a high ECW/TBW may affect the progression of cancer and immune function.

The fluid volume balance gradually changes with aging and various medical conditions. Consistent with past reports,[30] we have shown that a high ECW/TBW was significantly associated with older age and lower BMI. Several reports have identified that the change in ECW/TBW with aging is mostly because of the decreased cell volume due to organ aging, comorbidities that lead to fluid dysregulation, and sarcopenia.[31] However, a few reports mentioned that ECW/TBW might be increased in obese patients,[32] which is inconsistent with our findings. This inconsistency may be due to the different measurements for nutritional evaluation. Managing nutritional status based only on body weight, or even BMI, can be misleading, as it does not reflect real obesity or sarcopenia. We also showed that a high ECW/TBW was not associated with the TNM stage but with right-sided tumors. In general, cancer patients, especially those with metastasis, often induce excessive and unnecessary fluid retention, such as pleural effusion, ascites, or edema, in the peripheral extremities with or without major organ failure.[5] In addition, ECW/TBW can be changed by the cancer treatment and cancer progression. Considering these pieces of evidence, ECW/TBW might objectively evaluate the underlying host status, which cannot be detected by tumor staging in CRC patients without distant metastasis. Further, right-sided tumors, which tend to be more aggressive than left-sided tumors, are more likely to induce malnutrition, systemic inflammation, and anemia, leading to a high ECW/TBW. Past reports have shown that the immune microenvironment of right-sided tumors is characterized by increased infiltration of immune cells with enhanced cytotoxic function.[33] Since a high ECW/TBW may reflect preoperative immunodeficiency, immunological mechanisms according to the tumor location may be associated with ECW/TBW. Given these findings, it may be necessary to research the association of ECW/TBW with immune function in the tumor microenvironment.

ECW/TBW is also reportedly useful in evaluating the general condition of patients with increased fluid volume and a loss of intracellular mass, such as patients with heart failure, renal dysfunction, or hepatic dysfunction.[7–9] The balance between extracellular and intracellular osmolality is maintained via regulation of cell volume, which is critical because a disruption in cellular osmoregulatory

mechanisms can exacerbate disease unless an appropriate fluid replacement is given. ECW/TBW could be useful in estimating the onset of fluid retention in patients. Therefore, preoperative ECW/TBW might be able to detect patients who require adjustment of fluid content or physical condition before resection. However, in our study, there was no association between ECW/TBW and such comorbidities. This may be because the subjects were stable patients who underwent radical resection. Future subgroup analyses with a sufficient number of patients would be required to demonstrate the association between ECW/TBW and comorbidities in cancer patients.

As body composition plays a significant role in evaluating the patient's status, pretreatment evaluation and optimization of body composition may lead to improved clinical outcomes. However, there is no consensus on which method to measure and which index to use for these evaluations. Cancer patients experience loss of muscle mass, body cell mass, and TBW, and a change in fluid distribution with ECW expansion and reduced intracellular water (ICW). Recent reports have suggested that computed tomography (CT) can assess sarcopenia, visceral fat obesity, or sarcopenic obesity to predict recurrence and prognosis in CRC patients.[34,35] However, CT cannot measure body water which makes up about 60% of the body weight and cannot accurately evaluate the state of cachexia. The BIA evaluation is performed by sending a harmless electrical current through the body and can allow for estimating body composition easily and quickly. Since ECW/TBW was a significant predictor of recurrence independent of the TNM stage in our study, it may be effective to evaluate ECW/TBW in cancer treatments, the precondition of cachexia, using the easy-to-use BIA. To improve patient outcomes, fluid management using BIA (which may lead to managing nutrition, systemic inflammation, and anemia) might have better therapeutic effects.

This study has some limitations. First, as the study design was retrospective and only included data from a single institution, bias might have affected the results. Second, a relatively small number of patients ($n = 320$) was analyzed. During the study period, the study protocol was not fully understood by all the clinical staff members, so a number of patients were not measured by the bioelectrical impedance. Moreover, sometimes it was impossible to measure it because of insufficient staff number on the weekend or holidays. Also, the recurrence rate was relatively low, which may have resulted in bias. Third, the study period of 14 years is relatively long. However, we used the same device for measuring the bioelectrical impedance of the patients, so that the data of preoperative ECW/TBW are valid during the study period. Fourth, we have not shown the analysis using other body composition components for further characterization of a high ECW/TBW because our aim of this study was to clarify the clinical impact of preoperative ECW/TBW on CRC patient survival. Fifth, we did not validate the data using other independent cohorts. Sixth, body composition measured using BIA can be influenced by various factors, such as patient posture and preoperative fasting. Nonetheless, our results convincingly support previous findings and used a database of 320 CRC cases. In addition, this is the first study that evaluates the significance of ECW/TBW as a predictor of postoperative recurrence after potentially curative resection. Further validation studies are warranted to confirm our findings.

In conclusion, we have demonstrated that a high ECW/TBW was an independent predictor for recurrence and poor OS. Our data suggest that the preoperative evaluation of ECW/TBW using BIA might serve as a novel tool for developing CRC treatment strategies.

AUTHOR CONTRIBUTIONS

TH and RT described and designed the article. RT and YM edited the article. NY and HB supervised the edition of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

HB is an Editorial Board Member of *Annals of Gastroenterological Surgery*. There are no other potential conflicts of interest.

ETHICS STATEMENTS

Approval of the research protocol: The protocol of this study was approved by the human ethics review committee of the Graduate School of Medicine, Kumamoto University, and carried out according to the Declaration of Helsinki and Good Clinical Practice Guidelines.
Informed Consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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