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The Association Between Extracellular Water-to-Total Body Water Ratio and Therapeutic Durability for Advanced Lung Cancer

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Abstract. *Background/Aim: Extracellular water-to-total body water ratio (ECW/TBW) measured by bioelectrical impedance analysis (BIA) reportedly predicts clinical outcomes of various diseases. The aim of this retrospective study was to examine the association between ECW/TBW and therapeutic durability of chemotherapy and/or immune checkpoint inhibitors in advanced lung cancer. Patients and Methods: Patients with advanced lung cancer underwent BIA before chemotherapy and/or treatment with immune checkpoint inhibitors at our hospital between June 2018 and November 2019. Results: Of 75 patients, 18 with ECW/TBW ≥0.4 were assigned to the overhydrated group (OH-G) and 57 patients ECW/TBW <0.4 were assigned to the non-overhydrated group (NOH-G). The median time-to-treatment failure was significantly shorter in the OH-G than in the NOH-G (p=0.003). Multivariate analysis revealed that ECW/TBW ≥0.4 predicted treatment failure [hazard ratio (HR)=2.508, 95% confidence interval (CI)=1.19-5.27; p=0.01]. Conclusion: The ECW/TBW may be an objective parameter for predicting therapeutic durability in advanced lung cancer.*

The treatments for lung cancer have rapidly evolved, and the selection of a specific treatment strategy is typically based on various factors, including the patient's general condition (1, 2), as measured by the Eastern Cooperative Oncology Group performance status (ECOG PS) (3). Patients with good to moderate PS (PS 0-2) are expected to tolerate treatment well. However, PS is also subjectively assessed based on the clinician's judgement, which can introduce some heterogeneity. The Comprehensive Geriatric Assessment is a widely used method for evaluating the medical, psychological, and functional status of older patients (4), although its clinical application is limited by the substantial time needed for the valuation. Therefore, other objective parameters are needed to predict clinical outcomes. Bioelectrical impedance analysis (BIA) has recently attracted attention as a simple and non-invasive tool for objectively predicting clinical outcomes in cancer patients, by evaluating malnutrition and cancer cachexia (5, 6). The BIA evaluation is performed by sending a weak electrical current through the body and measuring related parameters (7, 8). Among the BIA parameters, the extracellular water to total body water ratio (ECW/TBW) is a useful indicator for nutritional assessments (7, 9), as it measures the body's water balance in the blood and interstitial fluid (*i.e.*, an edema index), with malnutrition being reflected in an increased proportion of extracellular water (9). A high ECW/TBW is also reportedly useful for identifying a poor general condition and predicting clinical outcomes among patients with chronic liver diseases (10-12), renal disorders (13, 14), heart failure (15, 16), and critical illness (9). However, we are not aware of any data regarding the relationship between ECW/TBW and lung cancer outcomes. Therefore, we aimed to clarify this relationship among patients who had received treatment for advanced lung cancer.

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Key Words: Lung cancer, bioelectrical impedance analysis, ECW/TBW, prognostic factor.

Patients and Methods

Patient selection and testing parameters. This retrospective study included patients with advanced lung cancer who received chemotherapy and/or immune checkpoint inhibitors at Osaka Habikino Medical Center between June 2018 and November 2019. However, patients who received molecular-targeted therapy for advanced lung cancer were excluded from this study.

Clinical records of the patients were reviewed to collect baseline data regarding age, gender, smoking status (never, former, current), ECOG PS (0-3), conditions that might affect the BIA readings (liver

dysfunction, renal disorders, and heart failure) (10-16), histology (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, others), disease stage (III, IV, recurrence) (17), treatment regimen, and previous lines of treatments (0/≥1). The initial treatment and all subsequent treatments were included in the analyses. Laboratory data were collected regarding lymphocyte count, the neutrophil-to-lymphocyte ratio, serum albumin (g/dl), and serum C-reactive protein (mg/dl).

BIA testing. A multi-frequency BIA scanner (InBody770; InBody, Seoul, Republic of Korea) was used to collect data regarding the patient's fat-free mass, total body water (TBW), extracellular water (ECW), and intracellular water. Segmental resistances were measured using eight surface electrodes at the thumbs, fingers, balls of the feet, and heels while the patient kept both arms abducted. Microprocessor-controlled switches and an impedance analyzer were activated in the sensors to measure segmental resistance at six frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1,000 kHz). These frequencies allow for separate measurements of intracellular and extracellular water, as low frequencies travel through extracellular water and cannot penetrate cell membranes, while high frequencies can penetrate cell membranes. Among the various BIA parameters, the present study evaluated the pre-treatment values for the ECW/TBW, with high values (*i.e.*, fluid overload) defined as ≥0.4 (11, 18-20). Using this cut-off point, the patients were classified into two groups: the overhydrated group (OH-G) with ECW/TBW ≥0.4 and the non-overhydrated group (NOH-G) with ECW/TBW <0.4.

Clinical outcomes. The outcomes of interest were the time-to-treatment failure (TTF), overall survival (OS), and severe adverse events. TTF was defined as the time from the BIA measurement to treatment failure owing to progressive disease (PD), severe adverse events, or deterioration of the patient's PS, within 1 year. The OS interval was calculated from the BIA measurement until death of the patient, within 1 year. Grade 3-4 adverse events during the first month after the BIA measurement were evaluated according to version 5.0 of the Common Terminology Criteria for Adverse Events (21). This observational period was selected in order to focus on the adverse events for 1 cycle of chemotherapy and/or immune checkpoint inhibitors.

Statistical analysis. Characteristics were compared between the two groups using the Mann-Whitney *U*-test and the Pearson's chi-squared test, as appropriate. The Kaplan-Meier method and log-rank test were used to compare the curves for TTF and OS. Furthermore, a Cox proportional hazard model was used to evaluate these outcomes, with the results reported as the hazard ratio (HR) and 95% confidence interval (CI). Differences were considered statistically significant at *p*-values of <0.05. All statistical analyses were performed using R software (version 3.3.2).

Ethical and consent to participate. The study's retrospective protocol was approved by the institutional review board of the Osaka Habikino Medical Center (formerly the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, Japan) on March 5, 2020 (approval no.: 1010). The requirement for informed consent was waived based on the retrospective design and use of anonymized data. All research protocols complied with the 1964 Declaration of Helsinki and its later amendments. Details regarding our center's opt-out policy are available at: http://www.ra.opho.jp/hospital/110/.

Table I. *Baseline characteristics of patients*.

	ECW/TBW of <0.4 (N=57)	ECW/TBW of ≥0.4 (N=18)	*p*-Value
Age, years			
Median (range)	72 (44-83)	77 (60-85)	1.00
Gender, n			
Male	44 (77.2%)	12 (66.7%)	0.37
Female	13 (22.8%)	6 (33.3%)	
ECOG PS, n			
0	11 (19.3%)	0 (0%)	0.001
1	40 (70.2%)	9 (50.5%)	
2	6 (10.5%)	8 (44.4%)	
3	0 (0%)	1 (5.6%)	
Smoking status, n			
Never	7 (12.3%)	6 (33.3%)	0.30
Current or former	50 (87.7%)	12 (66.7%)	
Conditions that might influence the BIA readings, n			
Yes	1 (1.8%)	1 (5.6%)	0.97
No	56 (98.2%)	17 (94.4%)	
Histological type, n			
Adenocarcinoma	33 (57.9%)	11 (61.1%)	0.40
Squamous cell carcinoma	11 (19.3%)	6 (33.3%)	
SCLC	9 (15.8%)	1 (5.6%)	
Others	4 (7.0%)	0 (0%)	
Stage, n			
III	10 (17.5%)	6 (33.3%)	0.30
IV	25 (43.9%)	8 (44.4%)	
Recurrence	22 (38.6%)	4 (22.2%)	
Treatment regimen, n			
CT	36 (63.2%)	15 (83.3%)	0.26
ICI	15 (26.3%)	3 (16.7%)	
CT plus ICI	6 (10.5%)	0 (0%)	
Treatment line, n			
1	34 (59.6%)	11 (61.1%)	1.00
≥2	23 (40.4%)	7 (38.9%)	
Lymphocyte count (/mm^3)			
Median (range)	1,380 (600-3,090)	1,170 (350-2,050)	0.176
Neutrophil-to-lymphocyte ratio			
Median (range)	3.25 (1.05-11.22)	3.99 (1.82-12.60)	0.169
Albumin (g/dl)			
Median (range)	4.00 (2.70-4.80)	3.60 (2.20-4.50)	0.002
C-reactive protein (mg/dl)			
Median (range)	0.32 (0.03-8.48)	0.48 (0.02-17.93)	0.51

ECOG PS: Eastern Cooperative Oncology Group performance status; ECW/TBW: extracellular water to total body water ratio; SCLC: small cell lung cancer; CT: chemotherapy; ICI: immune checkpoint inhibitor.

Results

Patient characteristics and laboratory findings. This study included 75 patients with advanced lung cancer and their baseline characteristics are shown in Table I. A total of 18

Table II. *Univariate and multivariate analyses of risk factors related to treatment failure.*

	Univariate analysis HR (95% CI)	*p*-Value	Multivariate analysis HR (95% CI)	*p*-Value
Age ≥75 years	1.29 (0.76-2.18)	0.34		
Gender Male	1.02 (0.56-1.85)	0.95		
ECOG PS of 2-3	1.63 (0.86-3.11)	0.135		
Current or former smoker	0.59 (0.31-1.13)	0.114		
Conditions that might influence the BIA readings	2.74 (0.66-11.38)	0.167		
Treatment using ICIs	0.99 (0.56-1.73)	0.96		
Treatment line of ≥2	1.27 (0.74-2.17)	0.39		
Serum albumin of ≤3.0 g/dl	2.27 (0.89-5.75)	0.085	1.48 (0.55-4.00)	0.44
ECW/TBW of ≥0.4	2.35 (1.30-4.23)	0.005	2.18 (1.16-4.08)	0.015

HR: Hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ECW/TBW: extracellular water to total body water ratio.

Table III. *Univariate and multivariate analyses of factors related to overall survival.*

	Univariate analysis HR (95% CI)	*p*-Value	Multivariate analysis HR (95% CI)	*p*-Value
Age ≥75 years	0.61 (0.24-1.54)	0.30		
Gender Male	1.53 (0.51-4.57)	0.45		
ECOG PS of 2–3	3.64 (1.48-8.96)	0.005	2.71 (0.95-7.72)	0.063
Current or former smoker	0.63 (0.23-1.74)	0.37		
Conditions that might influence the BIA readings	4.97 (0.64-38.68)	0.126		
Treatment using ICIs	0.40 (0.13-1.20)	0.104		
Treatment line of ≥2	1.77 (0.74-4.27)	0.20		
Serum albumin of ≤3.0 g/dl	3.13 (0.91-10.73)	0.070	1.83 (0.49-6.80)	0.37
ECW/TBW of ≥0.4	2.47 (1.01-6.06)	0.048	1.54 (0.56-4.27)	0.41

HR: Hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ECW/TBW: extracellular water to total body water ratio.

patients were assigned to the OH-G based on ECW/TBW ≥0.4 and 57 were assigned to the NOH-G based on ECW/TBW <0.4. The OH-G had a higher proportion of patients with a PS of 2-3 than the NOH-G (50.0% *vs.* 10.5%, $p=0.001$). Furthermore, the OH-G had a significantly lower median serum albumin concentration than the NOH-G ($p=0.002$). No other significant differences were observed in the clinicopathological characteristics between the two groups.

Relationship between the ECW/TBW and TTF. As shown in Figure 1, the OH-G had a significantly shorter median TTF than the NOH-G (1.9 *vs.* 4.9 months, HR: 2.35, 95% CI=1.30-4.23; log-rank $p=0.003$). Sixteen patients in the OH-G experienced treatment failure due to PD (10 patients, 62.5%), adverse events (4 patients, 25.0%), or a worsened general condition (2 patients, 12.5%). Forty patients in the NOH-G group experienced treatment failure; specifically, PD (n=28, 70.0%), adverse events (n=9, 22.5%), or a worsened general condition (n=3, 7.5%) were observed. The results of the multivariate analyses (Table II) revealed that the only independent predictor of treatment failure was the ECW/TBW (HR=2.51, 95% CI=1.19-5.27; $p=0.01$).

Relationship between the ECW/TBW and OS. Figure 2 shows that the NOH-G had significantly better OS than the OH-G (HR=2.47, 95% CI=1.01-6.06; log-rank $p=0.04$). The median OS was not reached in either group. In multivariate analysis, none of the examined factors was independently associated with OS (Table III).

Grade 3-4 adverse events during the first month. Table IV shows that the two groups did not have significantly different rates of Grade 3-4 adverse events during the first month after the BIA. However, the OH-G tended to have higher rates of non-hematological grade 3-4 adverse events, such as anorexia and infection.

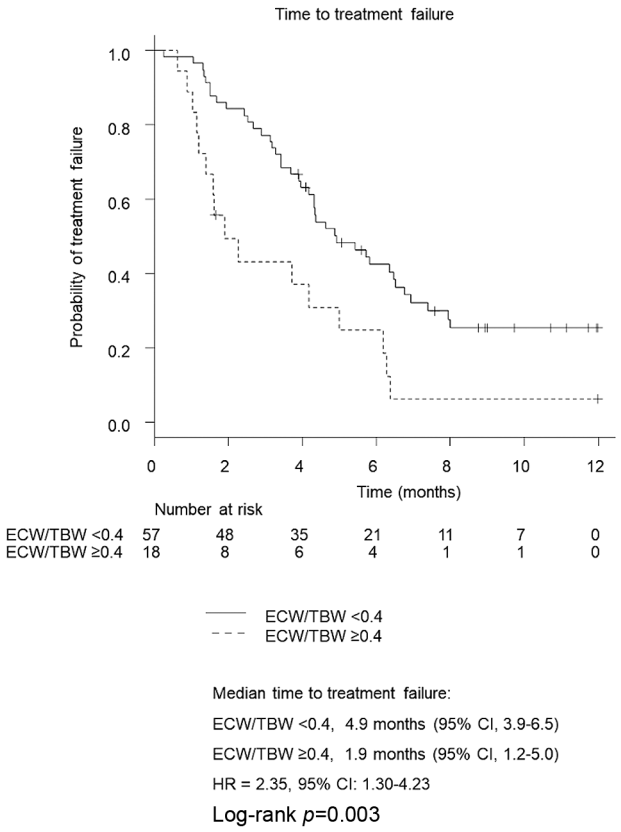

Figure 1. *Kaplan-Meier plot of the time-to-treatment failure according to the extracellular water-to-total body water ratio (ECW/TBW). HR: Hazard ratio; CI: confidence interval; NA: not available.*

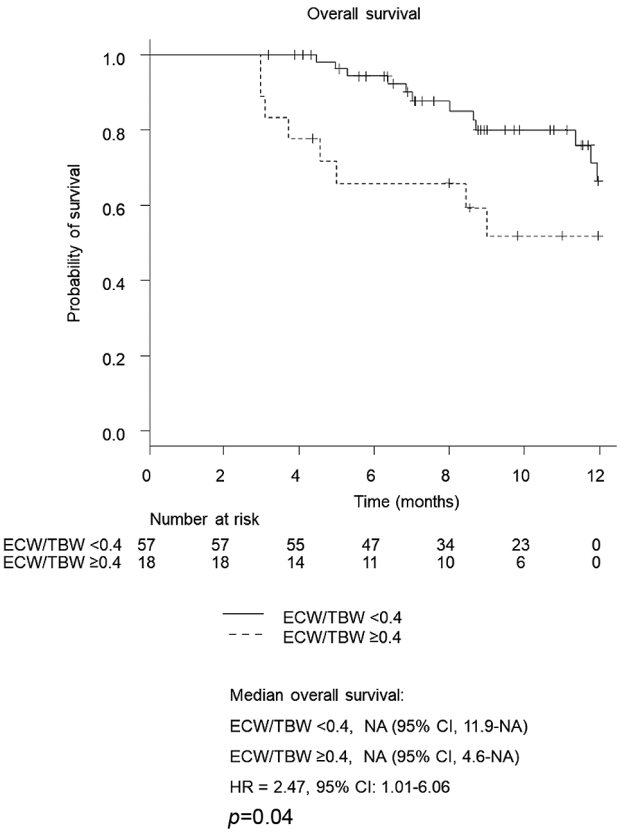

Figure 2. *Kaplan-Meier plot of the overall survival according to the extracellular water-to-total body water ratio (ECW/TBW). HR: Hazard ratio; CI: confidence interval; NA: not available.*

Table IV. *Treatment-related grade 3-4 severe adverse events.*

	ECW/TBW of <0.4 (N=57)	ECW/TBW of ≥0.4 (N=18)	*p*-Value
All events, n (%)	29 (50.9%)	10 (55.6%)	0.79
Hematological events, n (%)	23 (40.4%)	8 (44.4%)	0.79
Decreased white blood cell or neutrophil count	22 (38.6%)	7 (38.9%)	
Anemia	0 (0%)	1 (5.6%)	
Decreased platelet count	2 (3.5%)	0 (0%)	
Non-hematological events, n (%)	10 (17.5%)	6 (33.3%)	0.191
Nausea and anorexia	1 (1.8%)	2 (11.1%)	
Infection	4 (7.0%)	4 (22.2%)	
Gastric ulcer	1 (1.8%)	0 (0%)	
Increased alanine or aspartate aminotransferase	1 (1.8%)	0 (0%)	
Allergic reaction or anaphylaxis	2 (3.5%)	0 (0%)	

ECW/TBW: Extracellular water to total body water ratio.

Discussion

The present study revealed that an overhydrated state (ECW/TBW ≥0.4) predicted treatment failure of chemotherapy and/or immune checkpoint inhibitors among patients with advanced lung cancer. In addition, non-hematological grade 3-4 adverse events, such as anorexia and infection, were more common in the group with

ECW/TBW ≥0.4; however, this finding did not reach statistical significance. To the best of our knowledge, this is the first report to identify relationships between the ECW/TBW and clinical outcomes after treatment for advanced lung cancer.

Previous studies have indicated that the ECW/TBW is associated with clinical outcomes in cases involving chronic liver diseases, renal disorders, heart failure, and critical illness. This is because these conditions are mechanistically linked to extracellular osmolality. For example, advanced lung cancer leads to cachexia, which causes malnutrition and loss of skeletal muscle mass and function (*i.e.*, sarcopenia) (22, 23). This process leads to the loss of intracellular or body cell mass, with a corresponding expansion of extracellular mass. Other recent reports have also indicated that chronic inflammation may cause hyperosmotic stress, which involves an increase in extracellular osmolality, and plays an important role in carcinogenesis (24, 25). The balance between extracellular and intracellular osmolality is maintained via regulation of cell volume (*i.e.*, cell-volume homeostasis), which is critical because disruption of cellular osmoregulatory mechanisms can cause various diseases and complications (26). An increase in extracellular osmolality leads to intracellular dehydration, which results in structural damage to proteins that in turn causes altered enzymatic functions in the nucleus, mitochondria, and cytoskeleton (25, 27, 28). Accumulation of these changes and cell damage leads to apoptosis, which subsequently causes decreased muscle strength, gait instability, falls, fractures, respiratory infections, confusion, renal failure, increased medication toxicity, and an increased risk of death (25, 28, 29). Based on previous studies that have indicated an association between a high ECW/TBW and postoperative complications, such as infection (30, 31), we hypothesized that a high ECW/TBW might predict poor clinical outcomes after treatment for advanced lung cancer, and our findings appear to support this hypothesis.

Phase angle (PA) is an index of the healthy body cell mass and is used to evaluate a subject's nutritional status and potentially predict mortality in patients with various malignancies, including lung cancer (8, 32, 33). Nevertheless, the appropriate cut-off value for PA is unclear, as previous studies have used different cut-off values (6). In contrast, previous studies have indicated that the ECW/TBW of healthy persons is maintained at 0.38, with values of ≥0.4 in edematous persons (11, 18-20). As the ECW/TBW is reportedly related to the volume of lung cancer (34), we considered whether it might be a useful prognostic marker in patients who received treatment for advanced lung cancer. Our univariate analyses revealed significantly better OS in the OH-G than in the NOH-G, although the multivariate analyses failed to confirm that the ECW/TBW could independently predict OS at 1 year. The reasons for the lack of an independent association are not clear, although it is possible that the ECW/TBW should be considered a dynamic factor, rather than a static factor, as the value changes according to the patient's condition (31).

The present study has several limitations. First, the retrospective single-center design is prone to bias. Second, the small sample size may also be a source of bias. Third, we were not able to evaluate the patients' cardiac function, which might influence the ECW/TBW as an edema index. Further prospective studies are needed to confirm whether the ECW/TBW predicts long-term OS, or whether it exhibits dynamic changes according to the patient's general condition and treatment response.

In conclusion, ECW/TBW ≥0.4 was significantly associated with treatment failure at 1 year. Thus, ECW/TBW ≥0.4 may be an objective parameter for predicting the therapeutic durability for advanced lung cancer.

Conflicts of Interest

T.H. received honoraria and research funding from Ono Pharmaceutical Co. Ltd. (Osaka, Japan), Lilly Japan Co. Ltd. (Hyogo, Japan), AstraZeneca Co. Ltd. (Osaka, Japan), Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan), Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan), Merck Serono Co. Ltd. (Tokyo, Japan), MSD Oncology Co. Ltd. (Tokyo, Japan), Kyowa-Hakko Kirin, and Boehringer Ingelheim. The remaining Authors have no conflicts of interest to report.

Authors' Contributions

All Authors were involved in the study's conception and design; the data acquisition, analysis, or interpretation; drafting or revising the article for important intellectual content; and provided final approval of the submitted version. YN and TH collected the multi-frequency BIA data. YN and HS performed the statistical analyses.

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