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Segmental bioimpedance and arm-volume asymmetry after breast cancer surgery: a longitudinal analysis of within-patient associations

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Abstract

Background

Segmental bioimpedance and perometry assess different aspects of arm asymmetry after breast cancer surgery. The within-patient relationship between these measurements during extended postoperative follow-up remains incompletely characterized. We examined the association between segmental extracellular water/total body water (ECW/TBW) asymmetry and concurrent arm-volume asymmetry across postoperative periods.

Methods

This retrospective, exploratory cohort included 246 patients with 1,642 same-day perometry and segmental bioimpedance visits. Volume asymmetry was calculated as the affected-minus-unaffected arm volume divided by unaffected-arm volume, expressed as a percentage. ECW/TBW asymmetry was the affected-minus-unaffected arm ratio difference. Each patient's mean ECW/TBW asymmetry was separated from visit-specific deviations. Generalized estimating equations with working independence and patient-clustered robust standard errors adjusted for postoperative period, body mass index, nodal positivity, axillary surgery, and regional nodal irradiation. Sensitivity analyses examined exchangeable correlation and native perometry measurements. Secondary volume-course analyses included 2,045 visits from the same patients.

Results

A 0.01 higher ECW/TBW asymmetry relative to a patient's own mean was associated with 3.78 percentage points higher volume asymmetry (95% confidence interval [CI], 1.79–5.77). Beyond 3 years, the corresponding estimate was 3.86 (95% CI, 2.17–5.54). Associations differed across postoperative periods ($p = 0.00087$), with the largest estimate during 0–3 months, based on 35 patients and 46 visits. No clear evidence of heterogeneity was found among the three later periods ($p = 0.368$). Evidence of period heterogeneity in native-only paired measurements depended on working correlation. Adjusted volume asymmetry beyond 3 years was 9.48 percentage points higher than during 0–3 months (95% CI, 5.36–13.61), although the native-only contrast included zero under exchangeable correlation.

Conclusions

Segmental ECW/TBW asymmetry was positively associated with concurrent arm-volume asymmetry within patients, including beyond 3 years after breast cancer surgery. Period-specific estimates were sensitive to sparse early observations and analytic specification. These findings extend the

characterization of serial fluid-fraction and volume measurements during routine follow-up; their implications for surveillance decisions require prospective validation.

Background

Breast cancer–related lymphedema (BCRL) may develop or change over several years after treatment [1–4], making longitudinal assessment relevant to survivorship care [5, 6]. Objective follow-up has documented lymphedema 5 years after both sentinel lymph node biopsy and axillary lymph node dissection [7]. Perometry quantifies limb volume [8], whereas bioimpedance-based methods provide information about fluid distribution [9]. Axillary lymph node dissection and regional nodal irradiation are established risk factors [4, 10, 11], but postoperative volume and bioimpedance trajectories vary across patients [12, 13]. Prospective surveillance incorporating preoperative measurements has supported the detection and management of subclinical swelling [14].

Although volume-based and bioimpedance-based measurements are related, they assess different physical properties. Prospective comparisons of perometry with bioimpedance spectroscopy have demonstrated correlations alongside incomplete agreement in diagnostic classification [15, 16]. Multifrequency bioimpedance and perometry have also been compared for early detection [17], and longitudinal studies have described heterogeneous impedance-derived trajectories [18]. The present study used segmental multifrequency bioelectrical impedance analysis with InBody S20 and S10 devices to obtain arm-specific extracellular water/total body water (ECW/TBW) ratios. These fluid-fraction measurements are distinct from spectroscopy-derived L-Dex indices. Previous findings therefore provide context but do not directly establish how InBody-derived ECW/TBW asymmetry relates to perometric volume asymmetry within patients during extended postoperative follow-up.

An association across patients does not necessarily describe the relationship between repeated measurements within the same patient. Differences in body habitus, treatment, and limb size may contribute to between-patient correlations. Separating each patient’s mean ECW/TBW asymmetry from visit-specific deviations allows assessment of whether visits with fluid-fraction asymmetry above that patient’s own average also show greater volume asymmetry [19]. Including observations beyond 3 years permits assessment of this relationship during later postoperative care. Interpretation requires attention to clinically driven measurement timing and to the distinction between postoperative interarm asymmetry and relative volume change corrected for bilateral preoperative measurements [20].

In this retrospective longitudinal cohort, we examined whether visit-specific deviations in InBody-derived ECW/TBW asymmetry from each patient’s own mean were associated with concurrent perometric arm-volume asymmetry, and whether this association differed across postoperative periods, including beyond 3 years after surgery. Secondary analyses described the postoperative course of volume asymmetry, its associations with axillary surgery and recorded radiotherapy, and the direction of patient-level changes between early and late observation windows. All analyses were exploratory.

Methods

Study design and population

This retrospective longitudinal cohort study included 285 consecutive patients meeting the eligibility criteria at the Center for Breast Cancer, National Cancer Center, Republic of Korea. Patients underwent index breast cancer surgery between May 31, 2000, and October 8, 2020. Eligibility required unilateral breast cancer surgery with axillary staging or dissection, no preoperative systemic therapy, no de novo distant metastasis, and no synchronous contralateral breast surgery. Postoperative measurements obtained during routine clinical care through August 4, 2023, were considered for analysis.

Clinical characteristics were obtained from electronic medical records, the cancer registry, and manual record review. Final surgical pathology was prioritized when pathological information differed between sources. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [21]. The study protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center, Republic of Korea (IRB No. 2022-0397-0004). The requirement for informed consent was waived by the Institutional Review Board because of the retrospective design. Analysis datasets were de-identified using study identifiers and time relative to index surgery.

Follow-up and censoring

Measurements were obtained during routine clinical care rather than according to a fixed research schedule. Follow-up was censored at the earliest occurrence of disease recurrence, additional ipsilateral axillary surgery, or contralateral breast surgery. Measurements obtained after the censoring date were excluded.

Measurements

Arm volume was measured using optoelectronic perometry (Pero-System Messgeräte GmbH, Wuppertal, Germany) [8]. Measurements were obtained from native perometry output or recovered from electronic medical records and manually entered clinical records. All sources used the same anatomical measurement range, total arm-volume definition, and units. Measurement-source information was retained for sensitivity analyses.

Relative arm-volume asymmetry was calculated as 100 × (affected-arm volume − unaffected-arm volume) / unaffected-arm volume. The affected-minus-unaffected arm-volume difference, expressed in milliliters, was examined as a secondary outcome. Neither measure was corrected for preoperative interarm asymmetry; relative arm-volume asymmetry therefore differs from baseline-adjusted relative volume change [20, 22]. One implausible affected-arm volume was corrected after review of the original record.

Arm-specific extracellular water (ECW) and total body water (TBW) were assessed using segmental multifrequency bioelectrical impedance analysis (InBody Co., Ltd., Seoul, Republic of Korea). The InBody S20 was used through June 2014 and the InBody S10 from July 2014 onward. ECW/TBW asymmetry was calculated as the affected-arm ECW/TBW ratio minus the unaffected-arm ratio. These measurements were distinct from bioimpedance spectroscopy–derived L-Dex indices. Paired visits were defined as visits with perometry and bioimpedance measurements obtained on the same day. Positive asymmetry indicated greater volume or a higher ECW/TBW ratio in the affected arm.

Postoperative periods and covariates

Time since index surgery was categorized as 0–3 months, > 3–12 months, > 1–3 years, and > 3 years. Preoperative measurements were excluded from the longitudinal analyses.

Covariates included body mass index (BMI), nodal positivity, axillary surgery, and documented regional nodal irradiation (RNI). Nodal positivity indicated at least one metastatic lymph node. Axillary surgery was classified as any axillary lymph node dissection (ALND), including sentinel lymph node biopsy (SLNB) followed by ALND, or SLNB only. Paired-measurement models used visit-specific BMI. Perometry models used a patient-level BMI value recorded at the first paired visit; this value was not necessarily a preoperative measurement.

Radiotherapy was classified as none recorded, breast/chest-wall irradiation only, RNI, or an ambiguous field. In the reference models, the comparison group comprised all patients without documented RNI, including six patients with ambiguous fields. Radiotherapy dates were unavailable; consequently, RNI represented eventual recorded treatment rather than exposure status at each measurement. Treatment indicators reflected available records, and absence of documentation was not interpreted as confirmed non-administration.

Analysis populations

Of the 285 eligible patients, 265 had eligible perometry measurements, contributing 2,196 observations, including 74 preoperative measurements. Nine patients had preoperative measurements only, leaving 256 patients with 2,122 postoperative visits. Complete-case analysis excluded ten patients contributing 77 visits because of missing BMI (seven patients) or nodal-positivity status (three patients). All ten excluded patients had undergone ALND.

The perometry analysis dataset comprised 246 patients and 2,045 postoperative visits. The paired-measurement dataset included the same 246 patients and 1,642 same-day perometry and bioimpedance visits. Participant flow and analysis populations are presented in Additional file 1: Supplementary Figure S1 and Supplementary Table S1.

Statistical analysis

All analyses were exploratory. After reviewing initial analyses, generalized estimating equations (GEE) [23] with a Gaussian distribution, identity link, working independence, and patient-clustered sandwich standard errors were designated as the reference specification. Exchangeable working correlation with the same mean model was examined as a sensitivity analysis. This specification was selected post hoc. Analyses used the observed visits without weighting to account for observation frequency or timing.

Within-patient ECW/TBW–volume association

In the paired dataset, ECW/TBW asymmetry was multiplied by 100 and decomposed into each patient's mean across all included postoperative paired visits and each visit's deviation from that mean [19]. Relative arm-volume asymmetry was modeled as a function of these between-patient and within-patient components, postoperative period, visit-specific BMI, nodal positivity, RNI, and axillary surgery. Within-patient coefficients were expressed as the difference in volume asymmetry, in percentage points, per 0.01 higher ECW/TBW asymmetry relative to the patient's own mean.

A model without a period-by-deviation interaction estimated the common within-patient association. A separate model included this interaction to estimate period-specific associations, with an overall robust Wald test. Homogeneity across the three periods after 3 months was assessed separately. An additional model retained categorical-period main effects and included an interaction between the within-patient deviation and $\log_2$(years since surgery + 0.25). Its coefficient represented the difference in the within-patient slope per doubling of the quantity years since surgery + 0.25.

Patient means were calculated across the full postoperative paired record rather than separately within each period. The coefficients therefore describe contemporaneous associations with deviations from the patient mean, rather than associations between successive change scores or prediction of subsequent volume. Patients with only one paired visit had a within-patient deviation of zero. Sensitivity analyses examined native perometry measurements, additional adjustment for InBody device era, and restriction to S10-era measurements.

Secondary analyses of volume asymmetry

Relative arm-volume asymmetry was modeled using postoperative period, patient-level BMI, nodal positivity, RNI, and axillary surgery. Adjusted means were calculated by assigning each postoperative period to all observations, retaining their observed covariate values, and averaging the predicted values across visits. Standardization therefore used the visit-level covariate distribution rather than equal weighting of patients.

Period contrasts compared > 3 years with 0–3 months and with > 3–12 months. The affected-minus-unaffected volume difference was modeled directly using the same specification. Affected- and unaffected-arm volumes were also modeled separately. These estimates represent postoperative intervals rather than specific time points.

Clinical-factor and sensitivity analyses

Separate models examined period-by-factor interactions for ALND, RNI, and positive-node count. The ALND model adjusted for BMI, nodal positivity, and RNI; the RNI model adjusted for BMI, nodal positivity, and ALND; and the positive-node-count model adjusted for BMI, RNI, and ALND.

RNI analyses compared patients with documented RNI against three reference groups: all patients without documented RNI; patients without documented RNI after excluding ambiguous fields; and patients receiving breast/chest-wall irradiation only. Additional volume-course analyses were restricted to native perometry output, the first visit within each 6-month interval, or patients with measurements in both the early (0–12 months) and late (> 3 years) windows.

Descriptive patient-level changes

For patients with observations in both early and late windows, measurements were averaged within each window, and change was calculated as the late mean minus the early mean. Volume changes were summarized in the perometry subset, and changes in both modalities were summarized in the paired subset.

Among the 54 patients with paired measurements in both windows, 95% confidence intervals for mean volume-asymmetry change and the proportion with increased volume asymmetry but non-increased ECW/TBW asymmetry were obtained from 2,000 patient-level bootstrap resamples using the percentile method. These descriptive changes were distinct from the GEE period contrasts. Directional changes were classified relative to zero, without applying validated measurement-error or clinical thresholds.

No adjustment for multiple testing was applied. Effect estimates were reported with confidence intervals, and p values were interpreted as exploratory. All analyses were conducted using Stata version 19.0 (StataCorp, College Station, TX, USA).

Results

Study population

Of the 285 eligible patients, 246 contributed to the complete-case analysis cohort after exclusion of 20 patients without eligible perometry measurements, nine with preoperative measurements only, and ten with missing covariate data. The primary paired analysis included 1,642 same-day perometry and segmental bioimpedance visits, and the secondary volume-course analysis included 2,045 postoperative perometry visits from the same 246 patients (Supplementary Figure S1).

The mean age at surgery was 52.3 years (SD, 10.4); 189 patients (76.8%) had undergone ALND, 196 (79.7%) were node-positive, and 165 (67.1%) had documented RNI (Table 1). Patients contributed a median of six postoperative perometry visits (IQR, 4–11). The median interval from surgery to the last perometry measurement was 4.69 years (IQR, 2.32–8.05; range, 0.01–20.01), whereas the median

interval between the first and last postoperative perometry measurements was 2.67 years (IQR, 1.02–5.31).

The median number of paired visits was five per patient (IQR, 3–9); 240 patients had at least two paired visits, and six had one. The median interval between the first and last paired measurements was 2.26 years (IQR, 0.66–4.38). Across the four postoperative periods, the perometry dataset included 64 visits from 49 patients, 376 from 143, 528 from 143, and 1,077 from 166, respectively. Native perometry output accounted for 1,043 visits (51.0%), including 18 of 64 visits during 0–3 months and 628 of 1,077 visits beyond 3 years. Observation intervals, measurement counts, and unadjusted source-specific means are provided in Supplementary Tables S1 and S2.

Table 1
Characteristics of the total cohort and the primary analysis cohort

Characteristic	**Total cohort (n = 285)**	**Analysis cohort (n = 246)**
Age at surgery, years, mean (SD)	51.6 (10.2)	52.3 (10.4)
BMI, kg/m², mean (SD) [n with data]	25.0 (3.9) [254]	25.0 (3.9) [246]
Left-sided	156 (54.7%)	135 (54.9%)
Breast-conserving surgery	210 (73.7%)	187 (76.0%)
Mastectomy	69 (24.2%)	55 (22.4%)
Breast surgery type missing	6	4
SLNB only	62 (21.8%)	57 (23.2%)
Any ALND	223 (78.2%)	189 (76.8%)
primary ALND	188 (66.0%)	157 (63.8%)
SLNB followed by ALND	35 (12.3%)	32 (13.0%)
Node-positive, n/n with data (%)	220/282 (78.0%)	196/246 (79.7%)
Positive nodes, median (IQR)	2 (1–3)	2 (1–3)
Radiotherapy: RNI	188 (66.0%)	165 (67.1%)
Radiotherapy: breast/chest wall only	63 (22.1%)	54 (22.0%)
Radiotherapy: none recorded	25 (8.8%)	21 (8.5%)
Radiotherapy: ambiguous field	9 (3.2%)	6 (2.4%)
Chemotherapy recorded	213 (74.7%)	179 (72.8%)
Endocrine therapy recorded	157 (55.1%)	132 (53.7%)
HER2-targeted therapy recorded	43 (15.1%)	33 (13.4%)

BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RNI, regional nodal irradiation. Treatment variables are recorded indicators; 0 may reflect an absent record. Ten patients (all with ALND) were excluded from the analysis cohort for missing BMI or nodal-positivity status. Percentages are of all patients unless a denominator is shown. SD, standard deviation; IQR, interquartile range; HER2, human epidermal growth factor receptor 2. BMI is not necessarily a preoperative measurement.

Within-patient association between ECW/TBW and volume asymmetry

Across the 1,642 paired visits, ECW/TBW asymmetry that was 0.01 higher than a patient's own postoperative mean was associated with 3.78 percentage points higher concurrent volume asymmetry (95% CI, 1.79–5.77). The corresponding estimate under exchangeable working correlation was 3.82 percentage points (95% CI, 1.81–5.83).

Period-specific estimates were 12.08 percentage points (95% CI, 8.11–16.06) during 0–3 months, 5.67 (2.57–8.76) during > 3–12 months, 2.38 (− 1.18 to 5.93) during > 1–3 years, and 3.86 (2.17–5.54) beyond 3 years (Fig. 1; Table 2). These coefficients used patient means calculated across the full postoperative paired record. Associations differed across the four periods (Wald p = 0.00087), with the largest estimate occurring during 0–3 months, which included 35 patients and 46 visits. The test restricted to the three later periods did not provide clear evidence of heterogeneity (p = 0.368). The interaction with $\log_2$-transformed time was also inconclusive (coefficient, 0.04; 95% CI, − 1.15 to 1.22; p = 0.95).

Table 2
Within-patient ECW/TBW–volume associations by postoperative period

Period	Patients / visits	Working independence (reference)	Exchangeable (sensitivity)
0–3 months	35 / 46	12.08 (8.11–16.06)	15.99 (13.05–18.94)
> 3–12 months	118 / 276	5.67 (2.57–8.76)	5.10 (2.64–7.56)
> 1–3 years	128 / 416	2.38 (− 1.18–5.93)	2.15 (− 1.27–5.56)
> 3 years	166 / 904	3.86 (2.17–5.54)	4.04 (2.48–5.59)
Common slope	246 / 1,642	3.78 (1.79–5.77)	3.82 (1.81–5.83)
Overall period interaction, Wald p		0.00087	1.3×10^{-10}
Homogeneity across later three periods, p		0.368	0.356

Values are coefficients (95% confidence intervals), in volume-asymmetry percentage points per 0.01 higher within-patient ECW/TBW asymmetry. Estimates are from GEE with patient-clustered robust

standard errors; models include the patient mean and within-patient deviation of ECW/TBW asymmetry, period, BMI at visit, node-positive status, RNI, and any ALND. Continuous log2-time interaction: 0.04 (−1.15 to 1.22), p = 0.95. ECW/TBW, extracellular water/total body water; GEE, generalized estimating equations; BMI, body mass index; RNI, regional nodal irradiation; ALND, axillary lymph node dissection. The common slope comes from a model without the period-by-deviation interaction. Later-period homogeneity excludes 0–3 months. Patient means use all postoperative paired visits. Period coefficients are not estimates from separately centered period-only datasets. There were 240 patients with at least two paired visits and six with one.

Under exchangeable working correlation, the 0–3-month estimate was 15.99 percentage points (95% CI, 13.05–18.94), and the overall period-interaction p value was 1.3×10^{-10}. Adjustment for device era yielded a common slope of 3.81 (95% CI, 1.80–5.83; period-interaction p = 0.00013). Restriction to S10-era measurements, comprising 239 patients and 1,538 visits, yielded a common slope of 4.10 (95% CI, 1.71–6.50; period-interaction p = 0.0011).

In native-only paired data, comprising 210 patients and 1,043 visits, evidence for period heterogeneity depended on working correlation (p = 0.024 under independence and p = 0.38 under exchangeable correlation). Additional model and device-era sensitivity results are reported in Supplementary Table S3. Within-patient deviation IQRs were smaller than the 0.01 unit used to report coefficients (Supplementary Table S4).

Postoperative course of arm-volume asymmetry

Adjusted mean volume asymmetry was 6.7% (95% CI, 3.8–9.6) during 0–3 months, 6.4% (5.1–7.8) during > 3–12 months, 10.6% (8.5–12.7) during > 1–3 years, and 16.2% (13.1–19.3) beyond 3 years (Fig. 2A; Table 3). Point estimates were similar during the first two periods and higher during the later periods.

Compared with 0–3 months, adjusted asymmetry beyond 3 years was 9.48 percentage points higher (95% CI, 5.36–13.61). Compared with > 3–12 months, the difference was 9.75 percentage points (95% CI, 6.64–12.86). The directly modeled affected-minus-unaffected volume difference was 188 mL higher beyond 3 years than during 0–3 months (95% CI, 92–284) and 205 mL higher than during > 3–12 months (95% CI, 131–278).

In separate models, adjusted mean affected-arm volume was 2.38 L during 0–3 months and 2.59 L beyond 3 years. Corresponding unaffected-arm volumes were 2.23 L and 2.24 L (Fig. 2B).

Table 3
Adjusted relative volume asymmetry by postoperative period and period contrasts A. Adjusted mean relative volume asymmetry

Period	Perometry patients / visits	Paired patients / visits	Adjusted mean asymmetry, % (95% CI)
0–3 months	49 / 64	35 / 46	6.71 (3.78–9.64)
> 3–12 months	143 / 376	118 / 276	6.44 (5.06–7.83)
> 1–3 years	143 / 528	128 / 416	10.58 (8.49–12.68)
> 3 years	166 / 1,077	166 / 904	16.19 (13.07–19.32)

B. Period contrasts under the reference and sensitivity specifications

Contrast	Relative asymmetry, percentage points (95% CI)	Affected-minus-unaffected volume difference, mL (95% CI)
> 3 years vs 0–3 months	9.48 (5.36–13.61)	188 (92–284)
> 3 years vs > 3–12 months	9.75 (6.64–12.86)	205 (131–278)
Native only: >3 years vs 0–3 months, independence	7.01 (1.39–12.62)	156 (37–276)
Native only: >3 years vs 0–3 months, exchangeable	2.89 (− 3.02–8.80)	71 (− 46–187)

Perometry model: 246 patients, 2,045 visits. GEE (Gaussian, identity link) with working independence and patient-clustered robust standard errors, adjusted for BMI, node-positive status, RNI, and any ALND; means are standardized to each visit's observed covariates. Volume differences were modeled directly. Exploratory analysis. CI, confidence interval; GEE, generalized estimating equations; BMI, body mass index; RNI, regional nodal irradiation; ALND, axillary lymph node dissection. Each period pools all eligible visits within its interval.

Associations with axillary surgery, radiotherapy, and nodal burden

Exploratory period-by-factor interactions were observed for ALND ($p = 9.2 \times 10^{-5}$) and documented RNI ($p = 4.2 \times 10^{-6}$). Evidence for a positive-node-count interaction was inconclusive ($p = 0.062$). Beyond 3 years, adjusted volume asymmetry was 11.63 percentage points higher in the ALND group than in the SLNB-only group (95% CI, 3.37–19.89). Four-period estimates and overall interaction tests are presented in Supplementary Table S5.

The corresponding RNI contrast was 8.36 percentage points against all patients without documented RNI (95% CI, 2.80–13.92) and 8.27 against patients receiving breast/chest-wall-only radiotherapy (95% CI, 1.09–15.46). Under exchangeable working correlation, the latter estimate was 6.15 percentage points (95% CI, − 0.05 to 12.35). RNI classification sensitivity analyses are provided in Supplementary Table S6A. Some ALND–RNI combinations contained few patients, particularly during the earliest period (Supplementary Table S6B).

Sensitivity analyses and patient-level changes

In native-perometry data, the > 3-year versus 0–3-month contrast in relative asymmetry was 7.01 percentage points under working independence (95% CI, 1.39–12.62) and 2.89 under exchangeable correlation (95% CI, − 3.02 to 8.80). Corresponding contrasts in the directly modeled interarm volume difference were 156 mL (95% CI, 37–276) and 71 mL (95% CI, − 46 to 187), respectively. The source-by-period interaction p value was 0.053; these results did not establish equivalence of temporal patterns across recording sources.

Using the first visit in each 6-month interval, the > 3-year versus 0–3-month asymmetry contrast was 9.98 percentage points (95% CI, 6.49–13.47). Restriction to 77 patients with perometry measurements in both the early (0–12 months) and late (> 3 years) windows yielded a model-based contrast of 12.90 percentage points (95% CI, 8.32–17.48). These contrasts and those using > 3–12 months as the reference are reported in Supplementary Table S7.

Among 54 patients with paired measurements in both windows, the mean patient-level early-to-late change in volume asymmetry was + 8.45 percentage points (bootstrap 95% CI, 5.31–11.86), and the mean ECW/TBW asymmetry change was + 0.0032. Volume asymmetry increased in 41 patients; 15 of these patients had no increase in ECW/TBW asymmetry. This pattern occurred in 27.8% of the 54 patients (bootstrap 95% CI, 16.7–40.7%) and in 36.6% of the 41 patients with increased volume asymmetry. Among all 77 patients with perometry in both windows, the mean patient-level change in volume asymmetry was + 8.71 percentage points. These descriptive changes compared each patient’s window-specific means and were distinct from the model-based period contrasts (Supplementary Table S8).

Discussion

The principal finding of this study was a positive contemporaneous association between within-patient ECW/TBW asymmetry and arm-volume asymmetry during routine follow-up after breast cancer surgery. At visits when ECW/TBW asymmetry was higher than a patient’s own postoperative mean, volume asymmetry was also higher after adjustment for postoperative period and recorded clinical covariates. The association was observed across the paired dataset and remained positive at visits beyond 3 years. These findings describe concurrent variation around an individual’s average measurement; they do not demonstrate that fluid asymmetry precedes or causes subsequent volume change.

Earlier prospective studies evaluated both continuous correlations and diagnostic agreement between perometry and impedance-based measurements [15–17]. The present study extends this work by separating within-patient from between-patient variation in segmental ECW/TBW asymmetry using repeated same-day measurements across multiple postoperative periods. This distinction matters because an association between patients with different limb characteristics does not necessarily describe how measurements vary within an individual. Smoot et al. [18] reported heterogeneous bioimpedance resistance-ratio trajectories during the first postoperative year, whereas our analysis addressed the concurrent association between fluid-fraction asymmetry and volume asymmetry within patients over a longer observation period. The measurements used here were obtained with InBody S20 and S10 segmental multifrequency BIA. They are analytically distinct from spectroscopy-derived L-Dex, and diagnostic thresholds or performance estimates from BIS studies should not be directly transferred to these results.

The common within-patient association was similar under the two working-correlation specifications, after adjustment for device era, and in S10-era measurements alone. In contrast, period-specific findings were less stable. The largest coefficient occurred during the first 3 months, when only 35 patients contributed 46 paired visits. Its magnitude varied with working correlation, and evidence for period heterogeneity in native-only measurements depended on the specification. Tests restricted to the three later periods and the log-time interaction did not provide clear evidence of temporal differences, but they do not establish equivalent slopes. Thus, the findings do not support a progressively weakening association over postoperative time.

The scale and centering of these coefficients also require consideration. The 0.01 reporting unit exceeded the within-patient deviation IQR in each period and should not be interpreted as a typical fluctuation or a clinically validated threshold. Moreover, patient means were calculated across all available postoperative paired visits. The coefficient beyond 3 years therefore describes associations at late visits relative to each patient's overall observed mean, rather than an association estimated using a separately centered late-only record.

Secondary analyses showed higher adjusted volume asymmetry beyond 3 years than during the first postoperative year, consistent with previous reports of morbidity evolving over several years [3, 4, 7, 24]. The directly modeled interarm volume difference and the separately modeled arm volumes provided complementary descriptions of this pattern. The higher late-period asymmetry was accompanied by a higher adjusted affected-arm volume, while unaffected-arm point estimates were similar between the earliest and latest periods. However, native-only contrasts were sensitive to working correlation. The magnitude of the late-period difference therefore cannot be regarded as independent of recording-source composition and model specification. These interval comparisons also do not establish continuous progression within every patient.

Exploratory associations with ALND and documented RNI provide clinical context. Previous prospective surveillance studies have linked axillary treatment and regional nodal irradiation with lymphedema risk

[11, 25]. In the present cohort, early negative group contrasts, sparse combinations of ALND and RNI, absent bilateral preoperative correction, and clinically driven measurement timing complicate interpretation. RNI represented eventual recorded treatment because radiotherapy dates were unavailable; its association cannot be interpreted as a change occurring after irradiation. Evidence for period modification by positive-node count was inconclusive. Previous reports relating nodal burden to persistent lymphedema addressed a different outcome [26], and our findings do not establish an independent temporal effect of nodal burden.

Among 54 patients with paired measurements in both early and late windows, 15 had increased volume asymmetry without increased ECW/TBW asymmetry. This pattern illustrates directional heterogeneity within a selected subset, despite the positive average within-patient association. It does not establish that BIA failed to detect clinically meaningful progression, because changes were not classified using validated measurement-error thresholds or linked to symptoms and treatment decisions. Nor can these measurements distinguish extracellular-fluid accumulation from fat deposition or fibrosis. ECW/TBW is a fraction: an unchanged ratio does not necessarily indicate unchanged absolute extracellular water. Tissue-specific measurements and absolute fluid estimates would be needed to evaluate these explanations.

Strengths and clinical implications

Strengths include repeated same-day measurements, explicit separation of within-patient and between-patient associations, and observations extending beyond 3 years. Sensitivity analyses examined working correlation, recording source, device era, observation density, and radiotherapy classification. Together, these analyses help distinguish findings that were relatively consistent from those that depended on analytic choices.

The clinical contribution concerns the interpretation of serial measurements. Segmental ECW/TBW asymmetry and perometric volume asymmetry were related within patients, but the observed association alone does not establish individual-level agreement or interchangeability. Prospective surveillance and intervention studies emphasize linking objective assessment to actionable outcomes [5, 14, 24, 27]. Our study does not identify a diagnostic threshold, an optimal surveillance interval, or a clinical benefit from combined testing. Future validation should relate harmonized serial measurements to symptoms, functional limitations, treatment decisions, and subsequent outcomes.

Limitations

This retrospective single-center cohort used clinically driven measurements rather than scheduled research assessments. Observation timing may have depended on swelling, referral, or treatment response. Models fitted to observed visits and standardization over the visit-level covariate distribution gave greater representation to patients with more visits. Restricting measurements to one visit per 6-month interval reduced observation density but did not eliminate informative observation.

The reference GEE specification was selected after initial analyses, and some period-specific and native-only estimates depended on working correlation. Native and recovered perometry values represented the same measurement range, volume definition, and units; nevertheless, their contributions differed across postoperative periods, and record recovery could introduce transcription or selection errors. The source-by-period test did not establish equivalent temporal patterns. Likewise, device-era adjustment and S10-only analyses did not demonstrate calibration equivalence between InBody models.

Early paired observations were sparse, and ECW/TBW distributions differed across periods. Six patients with only one paired visit had a within-patient deviation of zero and therefore did not directly inform the within-patient slope. Patient means were estimated from records of differing duration and timing, and the median paired observation span was shorter than the interval from surgery to the last measurement. The early–late paired subset represented only 54 patients and may differ from patients without observations in both windows.

Complete-case exclusion of ten patients, all of whom had undergone ALND, may have introduced selection bias. Bilateral preoperative measurements were insufficient for a baseline-adjusted primary analysis. Longitudinal information on compression, decongestive treatment, symptoms, and tissue composition was unavailable. Recorded treatment indicators could also conflate non-administration with absent documentation. The findings therefore describe associations under observed routine care rather than untreated disease progression or causal treatment effects. All analyses were exploratory, and no adjustment was made for multiple testing.

Conclusions

Segmental ECW/TBW asymmetry above a patient's own postoperative mean was associated with greater concurrent arm-volume asymmetry, including at visits beyond 3 years. The common association was similar across several sensitivity analyses, whereas period heterogeneity and secondary volume-course estimates depended on sparse early observations, recording source, and model specification. These findings characterize within-patient measurement associations but do not establish diagnostic interchangeability, tissue mechanisms, or improved outcomes from combined surveillance.

Abbreviations

ALND
axillary lymph node dissection
BCRL
breast cancer-related lymphedema
BIA
bioelectrical impedance analysis
BIS
bioimpedance spectroscopy

BMI
body mass index
CI
confidence interval
ECW
extracellular water
ECW/TBW
extracellular water/total body water ratio
GEE
generalized estimating equations
IQR
interquartile range
RNI
regional nodal irradiation
SD
standard deviation
SLNB
sentinel lymph node biopsy
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TBW
total body water.

Declarations

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center, Republic of Korea (IRB No. 2022-0397-0004). The study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board because of the retrospective study design.

Consent for publication

Not applicable. The manuscript contains no identifiable individual-level information or images.

Competing interests

The authors declare that they have no competing interests.

Use of generative AI

During manuscript preparation, the authors used ChatGPT (OpenAI) to assist with language editing, drafting, and preparation of analysis and visualization code. The authors reviewed and verified the resulting text, code, and outputs and take full responsibility for the content of the manuscript.

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Author Contribution

SHC conceptualized the study. JSY and SHC developed the methodology. EJY performed the formal analysis. EJY and SHC conducted the investigation. SYJ, EGL, SL, HSK, JHH, JHH, THK, YJK, SHS, KSL, and HC contributed to data curation and validation. EJY and SHC prepared the visualizations. EJY drafted the manuscript. JSY and SHC critically reviewed and edited the manuscript. SHC supervised the study and coordinated project administration.

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Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to approval by the National Cancer Center Institutional Review Board and applicable institutional data-sharing policies.

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Figures

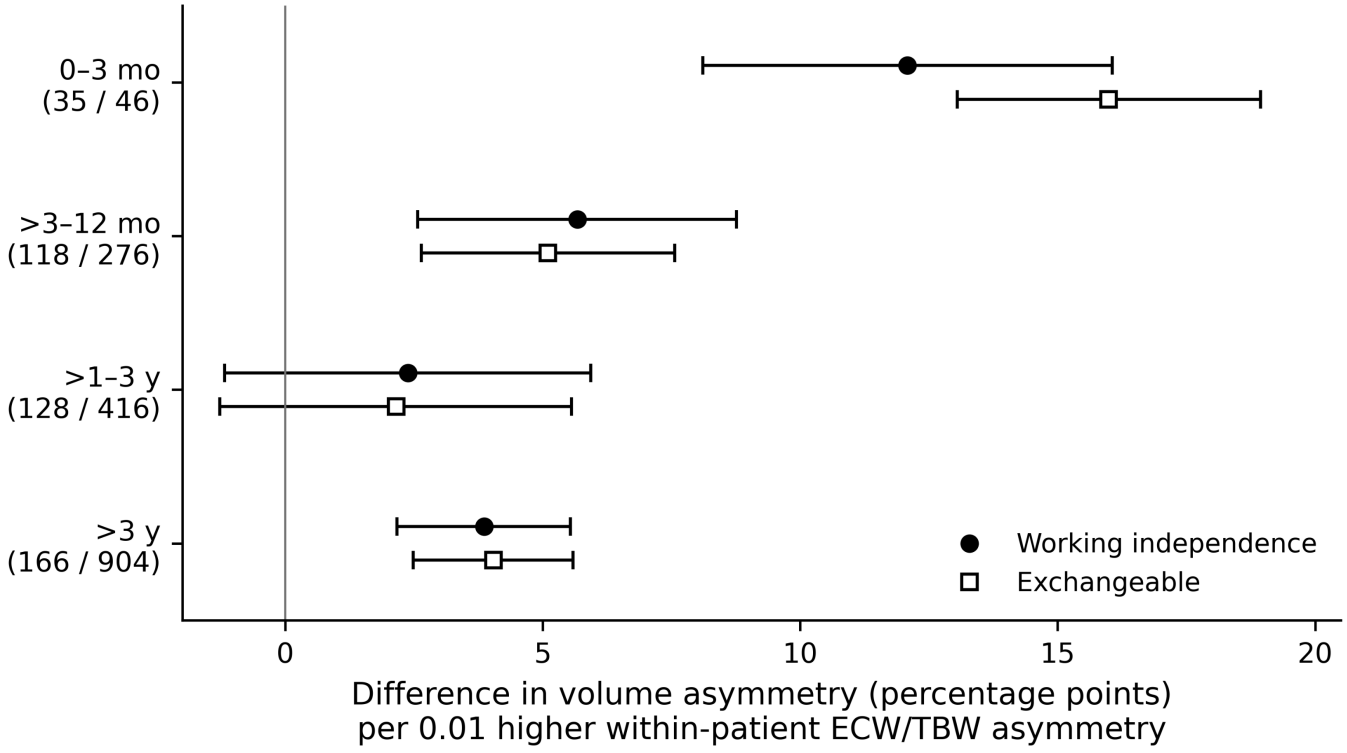


Figure 1

Period-specific within-patient ECW/TBW–volume associations. Coefficients are volume-asymmetry percentage points per 0.01 higher ECW/TBW deviation from the patient's mean across all postoperative paired visits (246 patients; 1642 visits). Bars show 95% confidence intervals; blue, working independence; orange, exchangeable correlation. Parentheses show patients / visits. Overall period interaction p=0.00087 and 1.3×10^{-10}, respectively; later-period homogeneity p=0.368 under independence.

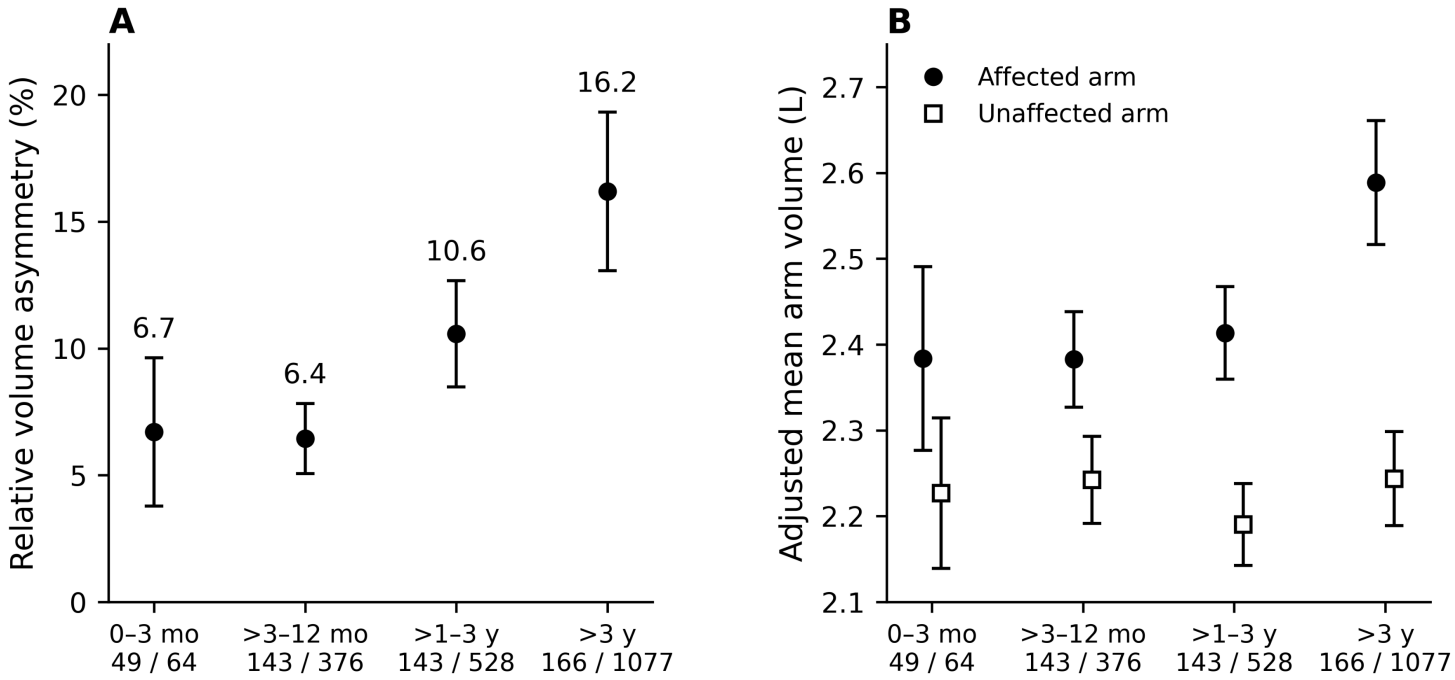


Figure 2

Adjusted relative volume asymmetry (a) and arm volumes (b) by postoperative period. Dots and bars show adjusted means and 95% confidence intervals (246 patients; 2045 visits). GEE used working independence, adjusting for BMI, nodal positivity, RNI, and ALND. Panel b uses separate arm-volume models; panel a is not the ratio of those means.

Supplementary Files

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