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The Effect of Neoadjuvant Chemotherapy on Breast Cancer-Related Lymphedema: A Prospective Clinical Trial

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Abstract

Background: Breast cancer-related lymphedema (BCRL) is a frequent complication that can impair the quality of life of survivors. While the effect of surgery and radiotherapy on lymphedema has been well established, the independent impact of neoadjuvant chemotherapy (NACT) on extracellular fluid remains unclear.
Methods: In this prospective clinical study, 111 patients with breast cancer scheduled for NACT were evaluated before and after chemotherapy. Arm circumferences and bioimpedance spectroscopy (BIS, L-Dex U400®) were performed pre- and post-NACT to assess extracellular fluid changes. A ≥6.5-unit increase in L-Dex was considered significant. Demographic, clinical, and pathological variables were analyzed using univariate and multivariate logistic regression.
Results: Extracellular fluid increase was detected in 18 patients (16.2%) after NACT, with no clinical lymphedema observed. In multivariate analysis, age ≥55 years (OR 4.47, 95% CI: 1.35–14.89; $p = 0.015$) and higher clinical N stage (OR 2.26, 95% CI: 1.16–4.43; $p = 0.017$) were independent predictors of extracellular fluid increase, whereas hormone receptor positivity was protective (OR 0.23, 95% CI: 0.07–0.72; $p = 0.012$).
Conclusions: NACT may contribute to subclinical extracellular fluid accumulation, particularly in older patients, those with advanced nodal disease, and those lacking hormone receptor positivity. Early BIS monitoring during chemotherapy may facilitate the detection of subclinical extracellular fluid changes and identify patients who may warrant closer surveillance for subsequent lymphedema.

Keywords: breast cancer, neoadjuvant chemotherapy, lymphedema, bioimpedance spectroscopy, extracellular fluid, risk factors

Introduction

Breast cancer is the most commonly diagnosed malignancy and remains the leading cause of cancer-related mortality among women worldwide. Despite significant reductions in mortality rates owing to advances in oncologic diagnosis and treatment, treatment-related morbidities continue to represent a major clinical challenge.[1] Among these, breast cancer-related lymphedema (BCRL) is a chronic and distressing condition that adversely affects patients' quality of life both physiologically and psychologically.[2]

BCRL is defined as the accumulation of protein-rich extracellular fluid in the interstitial tissue of the ipsilateral upper extremity following breast cancer treatment.[3] Etiologic factors include a high body mass index (BMI), sentinel lymph node biopsy (SLNB) or axillary dissection, a higher number of excised lymph nodes, axillary radiotherapy, chemotherapy, and the presence of capsular invasion in lymph nodes.[4,5]

Neoadjuvant chemotherapy (NACT) is widely used in patients with locally advanced—and increasingly, even early-stage—breast cancer, with the aim of assessing *in vivo* treatment response, reducing tumor size, expanding surgical options, and avoiding axillary dissection.[6,7] The chemotherapeutic agents used in NACT vary depending on tumor subtype (e.g., hormone receptor and HER2 status) and disease stage and may include Doxorubicin (Adriamycin), Cyclophosphamide, Paclitaxel, Docetaxel, Trastuzumab (Herceptin), Pertuzumab, and Carboplatin.[8]

The impact of chemotherapeutic agents on BCRL development remains controversial. Some studies suggest that taxane-based regimens may increase vascular permeability

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and interstitial fluid volume, thereby contributing to lymphedema.[9,10] However, existing research predominantly evaluates lymphedema in the postoperative setting. To date, no *in vivo* clinical study has specifically investigated the isolated effects of chemotherapeutic agents on lymphedema or extracellular fluid dynamics.

The aim of this study was to determine the effect of neoadjuvant chemotherapy—whose role in lymphedema development remains uncertain—on the volume of extracellular fluid, using both clinical measurements and bioimpedance spectroscopy.

Materials and Methods

Study design and participants

This prospective clinical study included patients diagnosed with breast cancer who were scheduled to receive neoadjuvant chemotherapy. Ethical approval was obtained from an institutional ethics committee, and written informed consent was obtained from all participants prior to inclusion.

Inclusion criteria.
- Age ≥18 years,
- Histologically confirmed breast cancer for which neoadjuvant chemotherapy was planned,
- Absence of any contraindication to bioimpedance measurement,
- Written informed consent for participation in the study.

Exclusion criteria.
- Discontinuation or incomplete completion of chemotherapy for any reason,
- Presence of clinical lymphedema prior to initiation of therapy,
- Use of a chemotherapy regimen differing from the predefined standard protocol.

Assessment of lymphedema and extracellular fluid. The primary objective was to determine whether neoadjuvant chemotherapy contributed to an increase in extracellular fluid and lymphedema in the treated upper extremity. For this purpose, arm circumference measurements and bioimpedance spectroscopy (BIS) assessments were performed both before chemotherapy initiation and 2 weeks after the final NACT cycle, immediately before surgery. This timing corresponded to the routine clinical interval between completion of NACT and surgery at our institution and allowed assessment after the completion of the final chemotherapy cycle rather than immediately following drug administration, when treatment-related acute effects may still be evolving.

Arm circumference measurement. Measurements of both upper extremities were obtained prior to NACT and repeated 2 weeks after treatment completion using a nonelastic flexible tape. With the patient's arm positioned comfortably, the olecranon was used as a reference point, and circumferences were measured at 5 cm intervals above and below this point. Measurements extended distally to the metacarpophalangeal joint and fingers and proximally to the axilla.

At each level, three consecutive measurements were taken and averaged. The tape was placed neither too tightly nor too loosely around the arm. A difference of ≥2 cm at any level between the two arms was considered clinically significant for lymphedema.[11]

All measurements were performed by a single physiotherapist who works at our Breast Center, is experienced in lymphedema management, and has received training in complex decongestive physiotherapy.

Bioimpedance spectroscopy (BIS). Bioimpedance measurements were performed using L-Dex U400® (ImpediMed, Australia), a segmental bioelectrical impedance spectroscopy device that objectively evaluates extracellular fluid and early lymphedema. Baseline measurements were recorded before NACT initiation and repeated 2 weeks after completion of chemotherapy.

All measurements were conducted by a single, experienced physiotherapist to ensure standardization.

Before each assessment, participants rested in the supine position for at least 10 minutes. Disposable surface electrodes were placed on the dorsum of both hands and the right foot.

The device delivered a low-level alternating current at frequencies between 1 and 75 kHz, measuring extracellular fluid resistance via tissue impedance. After initial readings, electrode connections on the upper extremities were alternated, and a second set of measurements was recorded to complete the session.

L-Dex values were automatically calculated by the device. A change of ≥6.5 units in L-Dex score from baseline to post-NACT was considered indicative of increased extracellular fluid.[12]

Neoadjuvant chemotherapy protocol. All patients received a standardized NACT regimen consisting of:

- Four cycles of intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days, followed by
- Weekly paclitaxel 80 mg/m^2 for 12 consecutive weeks.

For HER2-positive patients, targeted therapy was administered concurrently with paclitaxel as follows:

- Trastuzumab: Loading dose 8 mg/kg, followed by maintenance 6 mg/kg every 3 weeks,
- Pertuzumab: Loading dose 840 mg, followed by maintenance 420 mg every 3 weeks.

Demographic, clinical, and pathological variables. Baseline demographic and clinical parameters—including age, body mass index (BMI), tumor stage, clinical and radiological evaluations, and pathological features (hormone receptor and HER2 status)—were recorded prior to treatment. After NACT, follow-up data, including post-treatment BMI, clinical and radiologic response to chemotherapy, arm circumferences, and L-Dex scores, were documented.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed

using the Kolmogorov–Smirnov test. For comparisons between independent groups, the Mann–Whitney U test was used for non-normally distributed data, and the chi-square test (with Fisher's exact or Monte Carlo correction when appropriate) for categorical variables.

To identify independent predictors of extracellular fluid increase, multivariate logistic regression analysis (Forward: LR method) was performed after assessing for multicollinearity among variables. Results were reported as odds ratios [Exp(B)] with corresponding 95% confidence intervals (CI).

Descriptive statistics were expressed as mean ± standard deviation (SD) or median (minimum–maximum) for continuous variables and as number (percentage) for categorical variables.

Appropriate graphical representations were generated to visualize group distributions and relationships.

A p value <0.05 was considered statistically significant.

Results

Between January 2021 and May 2025, a total of 111 patients were prospectively enrolled and completed the study protocol. The mean age was 49.1 ± 10.5 years, and the mean BMI was 25.5 ± 3.7 kg/m^2. Demographic and clinical characteristics are summarized in Table 1.

The detailed characteristics of patients with and without extracellular fluid increase are presented in Table 2.

When patients with and without extracellular fluid accumulation were analyzed according to their molecular subtypes, the proportion of patients with extracellular fluid increase was significantly lower in the Luminal B group, whereas it was notably higher among those with triple-negative breast cancer (TNBC) (Table 2).

In the multivariate analysis performed to determine independent predictors of extracellular fluid accumulation, the following variables were included in the model: age ≥55 years, clinical N stage, molecular subtype, receptor subtype, hormone receptor positivity, and pathological T stage. The final regression model demonstrated a classification accuracy of 86.5%.

A higher clinical N stage (odds ratio [OR] = 2.26; 95% CI: 1.16–4.43; $p = 0.017$) and age ≥55 years (OR = 4.47; 95% CI: 1.35–14.89; $p = 0.015$) were identified as independent risk factors for extracellular fluid increase after neoadjuvant chemotherapy. Conversely, positive hormone receptor status was found to be a protective factor against extracellular fluid accumulation (OR = 0.23; 95% CI: 0.07–0.72; $p = 0.012$). Detailed univariate and multivariate regression results are summarized in Table 3.

Among the 18 patients who demonstrated a significant increase in extracellular fluid following NACT, all subsequently underwent axillary surgery. Ten patients (55.6%) underwent sentinel lymph node biopsy (SLNB) alone, three (16.7%) underwent axillary lymph node dissection (ALND) alone, and five (27.8%) underwent both SLNB and ALND. During the postoperative 1-year follow-up period, lymphedema was identified in 7 of these 18 patients (38.9%) based on clinical examination, arm circumference measurements, and L-Dex assessment. A difference of ≥2 cm at any measurement level between the two arms was considered clinically significant for lymphedema,[11] and all seven patients met this criterion. Of these 7 patients, 1 had undergone SLNB alone, 2 had undergone ALND alone, and 4 had undergone both SLNB and ALND. Thus, an ALND component was present in 6 of the 7 patients who subsequently developed lymphedema (85.7%). Among patients who underwent ALND, the number of lymph nodes removed ranged from 6 to 15.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (n = 111)

Variable	*Min–Max*	*Median*	*Mean ± SD/*n *(%)*
Age (years)	25.0–75.0	47.0	49.1 ± 10.5
<55 years			74 (66.7%)
≥55 years			35 (31.5%)
Body Mass Index (kg/m^2)	18.0–38.3	25.0	25.5 ± 3.7
Clinical T stage (cT)			
I			19 (17.1%)
II			72 (64.9%)
III			18 (16.2%)
IV			2 (1.8%)
Clinical N stage (cN)			
N0			14 (12.6%)
N1			64 (57.7%)
N2			22 (19.8%)
N3			11 (9.9%)
Pathological T stage (pT)			
T0			43 (38.7%)
T1			37 (33.3%)
T2			22 (19.8%)
T3			7 (6.3%)
T4			2 (1.8%)
Pathological N stage (pN)			
N0			63 (56.8%)
N1			34 (30.6%)
N2			6 (5.4%)
N3			8 (7.2%)
Number of positive lymph nodes	0–20	0	1.7 ± 3.3
Receptor subtype			
HR(+), HER2(–)			48 (43.2%)
HR(+), HER2(+)			29 (26.1%)
HR(–), HER2(+)			12 (10.8%)
Triple negative (TNBC)			22 (19.8%)
Molecular subtype			
Luminal A			15 (13.5%)
Luminal B			62 (55.9%)
HER2-enriched			12 (10.8%)
Triple negative			22 (19.8%)
Targeted therapy received			
No			70 (63.1%)
Yes			41 (36.9%)
Duration of treatment (days)	60–350	148	146.4 ± 35.3
Complete axillary response*			
No			46 (47.4%)
Yes			51 (52.6%)

Among the 111 patients followed prospectively, 18 patients (16.2%) demonstrated an increase in extracellular fluid (IEF) after completion of neoadjuvant chemotherapy. No patient showed a clinically significant difference in arm circumference or limb volume between sides.

HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Discussion

Previous studies investigating the impact of neoadjuvant chemotherapy (NACT) on lymphedema have reported inconsistent results. Most available data evaluate lymphedema after surgery and radiotherapy, which are well-established contributors to its development. However, to our knowledge, no study has specifically isolated the independent effect of chemotherapy itself on extracellular fluid changes.

Table 2. Comparison of Patients with and without an Increase in Extracellular Fluid (IEF) after Neoadjuvant Chemotherapy

Variable	*No IEF* (n = *93*)	*IEF* (n = *18*)	p *Value*
Age (years), mean ± SD	48.2 ± 9.9	53.4 ± 12.5	0.090
Age group, *n* (%)			**0.029**
<55 years	66 (89.2%)	8 (10.8%)	
≥55 years	27 (73.0%)	10 (27.0%)	
BMI (kg/m^2), mean ± SD			
Before chemotherapy	25.4 ± 3.6	26.1 ± 4.1	0.538
After chemotherapy	25.7 ± 3.9	26.2 ± 4.5	0.737
Clinical T stage (cT), *n* (%)			0.871
T1	16 (84.2%)	3 (15.8%)	
T2	60 (83.3%)	12 (16.7%)	
T3	17 (94.4%)	1 (5.6%)	
T4	0 (0%)	2 (100%)	
Clinical N stage (cN), *n* (%)			**0.040**
N0	14 (100%)	0 (0%)	
N1	55 (85.9%)	9 (14.1%)	
N2	17 (77.3%)	5 (22.7%)	
N3	7 (63.6%)	4 (36.4%)	
Pathological N stage (pN), *n* (%)			0.915
N0	53 (84.1%)	10 (15.9%)	
N1	29 (85.3%)	5 (14.7%)	
N2	5 (83.3%)	1 (16.7%)	
N3	6 (75.0%)	2 (25.0%)	
Number of positive lymph nodes (mean ± SD)	1.57 ± 3.24	2.22 ± 3.72	0.536
Treatment duration (days, mean ± SD)	145.4 ± 37.4	151.2 ± 21.0	0.390
Receptor subtype, *n* (%)			
HR(+), HER2(–)	43 (89.6%)	5 (10.4%)	0.148
HR(+), HER2(+)	27 (93.1%)	2 (6.9%)	0.113
HR(–), HER2(+)	9 (75.0%)	3 (25.0%)	0.382
Triple-negative (TNBC)	14 (63.6%)	8 (36.4%)	**0.004**
Molecular subtype, *n* (%)			
Luminal A	12 (80.0%)	3 (20.0%)	0.669
Luminal B	58 (93.5%)	4 (6.5%)	**0.002**
HER2-enriched	9 (75.0%)	3 (25.0%)	0.382
TNBC	14 (63.6%)	8 (36.4%)	**0.004**
Targeted therapy received, *n* (%)			0.379
No	57 (81.4%)	13 (18.6%)	
Yes	36 (87.8%)	5 (12.2%)	
Complete axillary response, *n* (%)+			0.991
No	38 (82.6%)	8 (17.4%)	
Yes	41 (80.4%)	10 (19.6%)	
Hormone receptor positivity, *n* (%)	69 (90.8%)	7 (9.2%)	**0.005**
HER2 positivity, *n* (%)	36 (87.8%)	5 (12.2%)	0.430

Bold values indicate statistically significant results ($p < 0.05$).

Among patients who developed IEF, 10 (55.5%) were aged 55 years or older, compared with 27 (29.0%) among those without IEF ($p = 0.029$). The proportion of patients with IEF was higher in the older age group.

In addition, 9 patients (50.0%) with IEF had clinical N2 or N3 disease before treatment, compared with 24 patients (25.8%) without IEF ($p = 0.040$).

IEF, increased extracellular fluid; BMI, body mass index; TNBC, triple-negative breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

In the present prospective study, an increase in extracellular fluid as detected by bioimpedance spectroscopy was observed in 16.2% of patients following NACT. Importantly, this subclinical change occurred without any measurable difference in limb circumference or volume, indicating early interstitial fluid accumulation before overt clinical lymphedema.

Extracellular fluid increase was significantly associated with older age (>55 years) and higher clinical N stage prior to treatment, while hormone receptor positivity appeared protective against this finding.

Age and lymphatic function

The relationship between age and lymphedema remains controversial in the literature. Chemotherapeutic agents, particularly taxanes, have been proposed to increase vascular permeability and interstitial fluid retention.[13,14] Swaroop et al. found no significant association between taxane-based chemotherapy and lymphedema but identified older age, higher BMI, and axillary dissection as independent risk factors.[10] In contrast, Jeong et al. demonstrated a higher incidence of lymphedema with taxane-containing regimens, as well as with antimetabolite and anthracycline agents.[15]

In our study, all patients received taxane-based chemotherapy, and one-third additionally received targeted HER2 therapies. Despite this, the presence of targeted therapy was not associated with extracellular fluid increase. The significant relationship between age ≥55 years and extracellular fluid accumulation may be explained by the combined effects of taxane-induced capillary hyperpermeability and age-related lymphatic dysfunction.[16,17]

Aging reduces lymphatic pumping capacity and increases vessel permeability through impaired junctional proteins and degradation of endothelial glycocalyx, leading to diminished lymphatic transport capacity and fluid clearance.[18–20]

While previous meta-analyses reported inconsistent findings regarding age as a risk factor, our results support the hypothesis that older patients are more susceptible to subclinical lymphatic overload even in the absence of surgical trauma.[21,22]

Although the relatively young age and lower BMI of our cohort may limit the generalizability of our findings to older and more obese breast cancer populations, these characteristics may also represent a strength in relation to the primary objective of the study. Our aim was specifically to evaluate extracellular fluid changes occurring during NACT, before surgery and radiotherapy. Studying a population with a relatively lower prevalence of established host-related lymphedema risk factors, particularly advanced age and obesity, may have reduced their contribution to extracellular fluid accumulation and allowed the changes occurring during NACT to be evaluated with less influence from these factors. Nevertheless, these findings should be validated in older and higher-BMI populations.

Nodal status and tumor burden

We also found a strong correlation between clinical N stage and extracellular fluid accumulation. Tumor invasion of axillary lymph nodes may impair lymphatic drainage and predispose to interstitial stasis. Several studies have confirmed that axillary nodal involvement, both preoperatively and postoperatively, is a significant predictor of lymphedema development.[23,24]

These findings are consistent with our observation that patients with N2–N3 disease had a higher likelihood of extracellular fluid increase after NACT, even before surgical intervention.

Hormone receptor status and tumor biology

The protective effect of hormone receptor positivity observed in our study may reflect differences in tumor biology and tissue microenvironment. Montagna et al. reported

Table 3. Univariate and Multivariate Logistic Regression Analysis of Factors Associated with an Increase in Extracellular Fluid (IEF)

	Univariate analysis			*Multivariate analysis*		
Variable	*OR*	*95% CI (lower–upper)*	p	*OR*	*95% CI (lower–upper)*	p
Age ≥ 55 years	2.875	1.022–8.086	**0.045**	4.476	1.346–14.885	**0.015**
Clinical N stage	2.215	1.220–4.090	**0.009**	2.264	1.157–4.430	**0.017**
Molecular subtype	1.692	0.935–3.102	0.082	—	—	—
Receptor subtype	1.706	1.055–2.757	**0.029**	—	—	—
Hormone receptor positivity	0.221	0.077–0.636	**0.005**	0.227	0.071–0.723	**0.012**

Bold values indicate statistically significant results ($p < 0.05$).
OR, odds ratio; CI, confidence interval.

an increased risk of lymphedema in ER-/HER2- tumors compared with ERBB2-positive cases.[25] Moreover, imaging-based studies have demonstrated that peritumoral edema is more common and more extensive in hormone receptor–negative breast cancers.[26,27]

Given that our study excluded surgical and radiotherapy-related effects, it is plausible that biological tumor aggressiveness influences lymphatic permeability and interstitial fluid retention.

Lymph node dissection and lymphedema

Among the 18 patients with a significant increase in extracellular fluid following NACT, 7 (38.9%) subsequently developed clinically evident lymphedema during postoperative 1-year follow-up. Notably, six of these seven patients (85.7%) had an ALND component. These findings suggest that early extracellular fluid accumulation following NACT may be relevant to subsequent lymphedema development, particularly in patients with additional treatment-related risk factors such as axillary lymph node dissection.

Other factors

Previous studies identified obesity as a significant risk factor for lymphedema.[28] In our cohort, however, no significant association was found between BMI and extracellular fluid increase, likely due to the relatively small number of obese participants (BMI > 30).

Additionally, the relatively young age and lower BMI of our cohort may limit the generalizability of our findings to older and higher-BMI breast cancer populations, who may have a greater baseline susceptibility to extracellular fluid accumulation and lymphedema.

Although median treatment duration was longer in patients with extracellular fluid increase, the difference was not statistically significant. This finding aligns with the report by Armer et al which emphasized the multifactorial nature of lymphedema risk following NACT and axillary treatment.[29]

Clinical Implications

Our study suggests that subclinical fluid retention may occur in a subset of patients receiving NACT even before surgical or radiotherapeutic interventions. Future research using BIS to assess extracellular fluid before and after NACT may provide important insights into the potential effect of NACT on breast cancer-related lymphedema and help clarify whether early extracellular fluid changes are associated with subsequent lymphedema development. Early detection of such changes may identify patients who could benefit from closer surveillance, especially in older or node-positive individuals.

Limitations

This study has several limitations. The sample size was moderate, and follow-up was limited to the preoperative period, precluding long-term evaluation of clinical lymphedema development. Furthermore, potential confounding factors such as subclinical inflammation or vascular effects of chemotherapy were not directly measured. Nonetheless, the prospective design, standardized BIS measurements, and homogeneous NACT protocol strengthen the validity of the findings.

Another limitation is that lymphatic function was not directly assessed in this study. Although bioimpedance spectroscopy provides an objective assessment of extracellular fluid changes, it does not directly evaluate lymphatic anatomy or lymphatic transport function. Therefore, the significant increase in extracellular fluid observed 2 weeks after NACT should not be interpreted as definitive evidence of lymphatic dysfunction or clinical lymphedema. ICG lymphography and lymphoscintigraphy were not performed in the present study. Future prospective studies incorporating lymphatic imaging techniques together with bioimpedance spectroscopy and longer-term clinical follow-up are warranted to determine whether early extracellular fluid increases following NACT are associated with subsequent lymphatic dysfunction and the development of lymphedema.

Conclusion

In summary, this prospective clinical study demonstrated that neoadjuvant chemotherapy was associated with a measurable increase in extracellular fluid in older, hormone receptor–negative, and clinically node-positive breast cancer patients. These findings highlight the importance of baseline and follow-up bioimpedance assessments during neoadjuvant therapy to identify subclinical changes and implement early lymphedema prevention strategies.

Authors' Contributions

Conceptualization: Z.E.I. Methodology: C.H. Data collection: C.H. Data curation: E.O. Formal analysis: E.K. Validation: E.K. Investigation: T.A.T. and V.O. Resources: V.O.

Writing—original draft: Z.E.I. and C.H. Writing—review and editing: All authors. Supervision: G.S. Project administration: Z.E.I. All authors read and approved the final article.

Ethics Approval

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Approval was granted by Bahçeşehir Univesity Ethics Committee for Non-Interventional Studies (Date: 05/02/2025/No: 2025-06/07).

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

Not applicable. No individual participant's data in any identifiable form are included in this article.

Author Disclosure Statement

The authors have no relevant financial or non-financial interests to disclose.

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