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Association of Tumor-Infiltrating Lymphocytes and Body Mass Index (BMI) in Early HER2-Positive Breast Cancer: Insights from the ShortHER Trial

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Abstract

Previous research from the ShortHER trial established the prognostic value of tumor-infiltrating lymphocytes (TILs) in patients with early-stage HER2-positive breast cancer. This study investigates the influence of body mass index (BMI) on the prognostic impact of TILs. The ShortHER trial compared 9 weeks versus 1 year of adjuvant trastuzumab combined with chemotherapy in 1253 patients with HER2-positive early breast cancer. BMI data at baseline were available for 1213 patients (excluding 34 underweight individuals). Key outcomes included disease-free survival (DFS), recurrence-free survival (RFS), distant disease-free survival (DDFS), and overall survival (OS). Competing risk analysis was used to evaluate the cumulative incidence of different event types.

Among the patients, 583 (48%) were normal weight, 360 (29.7 percent) overweight, and 236 (19.5 percent) obese. Survival outcomes (DFS, RFS, DDFS, OS) were comparable between normal-weight patients and those with overweight or obesity. In the subgroup with both TIL and BMI data (n=819), higher TIL levels (per 5% increment) independently predicted better DFS (P=0.003), RFS (P=0.001), and DDFS (P=0.018) in normal-weight patients. In overweight or obese patients, higher TILs were linked only to improved DDFS (P=0.044). Normal-weight patients with TILs ≥20% showed significantly better DFS (P=0.007), RFS (P=0.002), and DDFS (P=0.027) than those with TILs <20%. No such differences were observed in overweight/obese patients. Competing risk analysis revealed higher rates of locoregional (P=0.001) and distant recurrence (trend, P=0.07) in normal-weight patients with low TILs, while overweight/obese patients with low TILs had increased distant recurrence (P=0.005). These findings indicate that elevated BMI may reduce the local protective benefits of TILs—while preserving their distant protective effects—in overweight or obese patients with HER2-positive early breast cancer receiving adjuvant chemotherapy and trastuzumab.

Keywords: HER2-positive, Breast cancer, BMI, TILs

Introduction

In recent decades, treatment strategies for HER2-positive early-stage breast cancer have advanced significantly, achieving exceptionally high cure rates. Despite this progress, notable differences in patient outcomes remain, which traditional prognostic markers do not fully explain, underscoring the need for better tools to capture this variability. Tumor-infiltrating lymphocytes (TILs) have become a key emerging biomarker in this area, with numerous studies showing their ability to forecast survival in patients with HER2-positive early breast cancer undergoing adjuvant chemotherapy plus anti-HER2 therapy [1–9].

The ShortHER trial, a phase III randomized study, assessed whether a shorter course (9 weeks) of adjuvant trastuzumab combined with chemotherapy was non-inferior to the standard 1-year duration in patients with HER2-positive early breast cancer. Results from this trial highlighted the substantial independent prognostic value of TILs and hinted at a potential interplay with treatment length: patients with elevated TILs (≥20%) experienced

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no added risk of distant recurrence or mortality on the shorter regimen [10].

Excess body fat is a confirmed risk factor for developing breast cancer, especially after menopause [11, 12], mainly through heightened estrogen production from androgen conversion in adipose tissue and the fostering of persistent low-level inflammation. Additionally, women with obesity at breast cancer diagnosis generally face greater chances of relapse and death than those at normal weight [13–16]. This link is firmly established for hormone receptor-positive/HER2-negative subtypes, and evidence is mounting for HER2-positive cases as well [17–20].

Proposed explanations for obesity's negative influence on breast cancer outcomes involve disrupted inflammatory signaling, weakened immune responses against tumors, and alterations in the tumor microenvironment [16, 21]. Yet, practical ways to assess these factors and gauge their real-world effects are still limited.

This analysis examines whether excess adiposity—approximated by body mass index (BMI)—affects the prognostic significance of TILs, drawing on patient data from the ShortHER trial.

Materials and Methods

Study population

The ShortHER trial (EudraCT: 2007-004326-25; ClinicalTrials.gov Identifier: NCT00629278) was an Italian multicenter phase III randomized trial testing non-inferiority. Comprehensive information on design, inclusion criteria, protocols, and statistics has been reported elsewhere [22, 23].

Briefly, 1254 patients with resected HER2-positive breast cancer were allocated randomly to adjuvant trastuzumab for either 9 weeks (short arm, n=627) or 1 year (long arm, n=627), paired with chemotherapy. Regimens varied by arm: the long arm featured four cycles of anthracycline plus cyclophosphamide followed by four cycles of a taxane every 3 weeks; the short arm used three cycles of docetaxel every 3 weeks followed by three cycles of 5-fluorouracil, epidoxorubicin, and cyclophosphamide. Post-chemotherapy, radiation and hormone therapy were given as clinically appropriate. The initial primary endpoint analysis of disease-free survival (DFS) did not confirm non-inferiority for the short arm [22]. At longer-term follow-up, however, 10-year DFS and overall survival (OS) rates were virtually identical across arms [23].

Of the trial participants, 893 had samples suitable for TIL evaluation (441 in the long arm, 452 in the short arm). A prior evaluation at 6 years median follow-up identified a clear link between TILs and distant disease-free survival (DDFS) [24]. Updated results at 9 years median follow-up reinforced this and, notably, established TILs' prognostic role for OS in this setting for the first time—each 5% rise in TILs correlated with better DDFS (hazard ratio [HR] 0.87, 95% CI 0.80-0.95, P=0.001) and OS (HR 0.89, 95% CI 0.81-0.98, P=0.01)[10].

The study received approval from relevant ethics committees and adhered to Good Clinical Practice and Helsinki Declaration standards. Participants provided informed consent for research use of their tumor material. Reporting complied with CONSORT guidelines.

In these exploratory investigations, the BMI cohort encompassed patients with recorded BMI at randomization (underweight cases excluded), and the BMI-TIL cohort included those with both qualifying BMI and TIL measurements. Reasons for excluding underweight patients, plus patient counts, are explained in the 'Biomarker assessment' and 'Statistical analysis' sections.

Biomarker assessment

HER2 status and hormone receptor (HR) expression were determined at individual study sites. A tumor was classified as HR-positive if estrogen receptor (ER) and/or progesterone receptor (PR) staining was present in at least 10% of cells.

Body mass index (BMI) was calculated at the time of study entry using the formula: weight (in kilograms) divided by height (in meters) squared. Patients were grouped based on World Health Organization criteria: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥30 kg/m²).

Stromal tumor-infiltrating lymphocytes (TILs) were evaluated centrally on hematoxylin-and-eosin-stained sections from the primary tumor, following established international guidelines for TIL scoring [25]. Prior reports have described the evaluation process in detail, including high inter-observer agreement between the two pathologists (MVD and MS) [10].

Statistical analysis

This BMI-focused analysis included all patients with available BMI data at randomization (n=1213 out of 1253), so no formal power calculation was performed.

Key survival outcomes were defined as follows:

- Disease-free survival (DFS): interval from randomization to a second primary malignancy, locoregional recurrence, distant metastasis, or death from any cause.
- Recurrence-free survival (RFS): interval from randomization to locoregional recurrence, distant metastasis, or death.
- Distant disease-free survival (DDFS): interval from randomization to distant metastasis or death.
- Overall survival (OS): interval from randomization to death from any cause.

Underweight patients were excluded from analysis (n=34 in the full BMI cohort; n=21 in the subgroup with TIL data) due to their small numbers and known poorer prognosis [26, 27].

For examining BMI's prognostic effects, patients were grouped as normal weight versus overweight/obese.

To investigate TILs' prognostic value within BMI strata, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), treating TILs as a semi-continuous variable (per 5% increase). Survival probabilities were plotted using Kaplan-Meier estimates, with TILs dichotomized at a 20% threshold—for alignment with earlier ShortHER publications [10, 24], where this cutoff identified patients achieving ≥95% 5-year DDFS, considered low-risk. Additional cutoff explorations were conducted based on emerging patterns, especially in the overweight/obese group.

Cumulative incidence of initial event types was assessed via competing risks methods [28, 29], accounting for locoregional recurrence, distant metastasis, second primary malignancy, and death without prior recurrence as competing events. Patients without events were censored at last follow-up. Simultaneous locoregional and distant events as first occurrence were classified as distant.

Analyses were performed in SPSS version 29 (IBM Corp., Armonk, NY, USA). All tests were two-tailed, with $P<0.05$ denoting statistical significance.

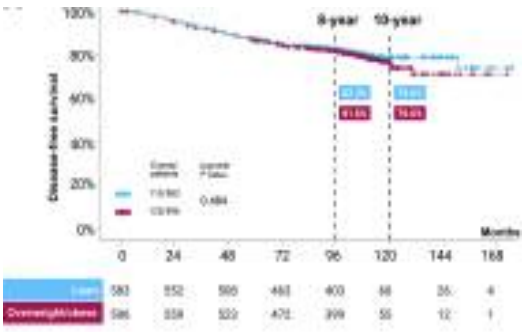
Results and Discussion

Patient characteristics and BMI's prognostic effects in the BMI cohort

The BMI cohort comprised 1179 patients with recorded BMI >18.5 kg/m² at randomization (representing 94.1% of the total ShortHER population).Distribution was: 583 normal-weight (49.4%), 360 overweight (30.6%), and 236 obese (20.0%).

Compared to normal-weight patients, those who were overweight or obese tended to be older, postmenopausal, with more advanced pathologic tumor stage (pT) and nodal status (pN), and higher rates of HR positivity. They also more frequently underwent breast-conserving surgery.

No significant differences in survival were linked to BMI category. Specifically, 10-year rates for normal-weight versus overweight/obese patients were: DFS 78.6% vs. 76.6% (P=0.484), RFS 81.5% vs. 81.3% (P=0.765), DDFS 86.3% vs. 84.3% (P=0.465), and OS 90.4% vs. 88.0% (P=0.151)—**Figures 1a-1d**. Treating BMI as continuous similarly showed no meaningful ties to DFS, RFS, or DDFS. However, continuous BMI was associated with OS on univariate testing (DFS: HR 1.01, 95% CI 0.99–1.04, P=0.360; RFS: HR 1.01, 95% CI 0.98–1.04, P=0.570; DRFS: HR 1.02, 95% CI 0.99–1.05, P=0.230; OS: HR 1.04, 95% CI 1.00–1.07, P=0.041).



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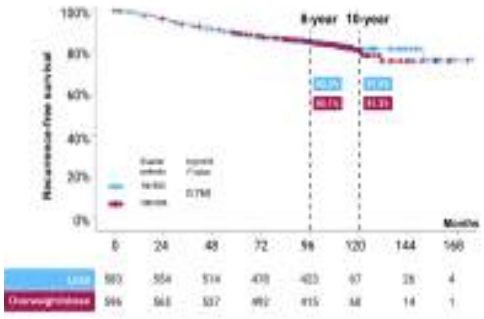

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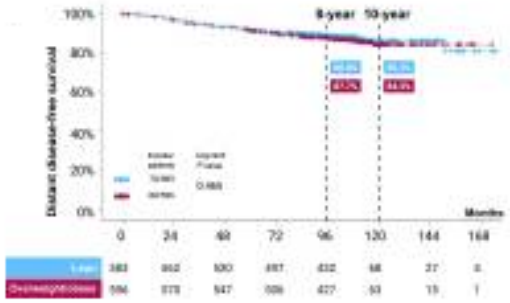

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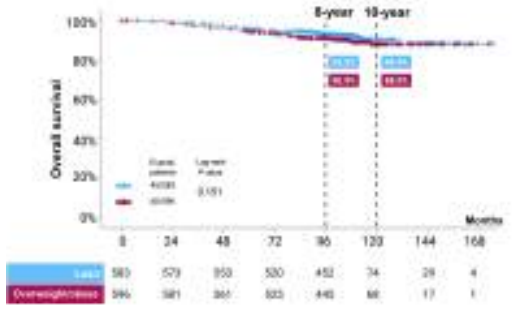

d)

Figure 1. Kaplan Meier curves according to BMI categories (lean versus overweight/obese). Panel (a) shows disease-free survival (DFS), (b) recurrence-free survival (RFS), (c) distant disease-free survival (DDFS), and (d) overall survival (OS). Across all panels, the survival curves for the two groups overlap substantially, indicating comparable outcomes.

Specifically, 10-year rates were: DFS 78.6% (normal weight) vs. 76.6% (overweight/obese, P=0.484); RFS 81.5% vs. 81.3% (P=0.765); DDFS 86.3% vs. 84.3% (P=0.465); and OS 90.4% vs. 88.0% (P=0.151).

Multivariable Cox regressions—adjusted for menopausal status, pathologic tumor size (pT), nodal status (pN), tumor grade, hormone receptor status, and treatment arm—confirmed no significant survival differences between normal-weight patients and those with overweight or obesity.

Prognostic associations of TILs stratified by BMI in the BMI+TIL cohort

The BMI+TIL subgroup consisted of 819 patients who had both evaluable TIL data and qualifying BMI from the main BMI cohort

This subgroup closely mirrored the full ShortHER population, though with marginally older median age and somewhat lower median TIL values.

BMI distribution in this subgroup: normal weight (n=410, 50.1%), overweight (n=246, 30.0%), obese (n=163, 19.9%).

In multivariable Cox models (adjusted for the same covariates as above; **(Table 1)**), higher TIL levels (modeled as per 5% increase) showed strong independent associations in normal-weight patients with better DFS (HR 0.839, 95% CI 0.746–0.943, P=0.003), RFS (HR 0.774, 95% CI 0.661–0.907, P=0.001), and DDFS (HR 0.831, 95% CI 0.711–0.970, P=0.019).

Table 1. Multivariate survival analysis stratified by TILs in lean versus overweight/obese patients

Variable	DFS		RFS		DDFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Lean patients								
TILs	0.839 (0.746–0.943)	0.003	0.774 (0.661–0.907)	0.001	0.831 (0.711–0.970)	0.019	0.914 (0.798–1.048)	0.198
Menopausal status (post vs. pre)	0.914 (0.563–1.483)	0.716	0.877 (0.520–1.479)	0.623	1.189 (0.651–2.169)	0.573	1.766 (0.814–3.830)	0.150
pT stage								
pT1	Reference	0.212	Reference	0.127	Reference	0.060	Reference	0.206
pT2	1.542 (0.945–2.516)	0.083	1.176 (1.010–2.917)	0.046	2.101 (1.136–3.886)	0.018	1.946 (0.912–4.149)	0.085
pT3–4	1.520 (0.453–5.096)	0.497	1.725 (0.506–5.878)	0.383	1.451 (0.327–6.440)	0.624	0.967 (0.121–7.720)	0.975
pN stage								
pN0	Reference	0.075	Reference	0.048	Reference	0.001	Reference	0.001

pN1	1.154 (0.674–1.977)	0.601	1.440 (0.806–2.574)	0.218	2.031 (1.012–4.074)	0.046	1.675 (0.677–4.141)	0.264
pN2–3	2.076 (1.098–3.925)	0.025	2.358 (1.189–4.677)	0.014	4.077 (1.909–8.706)	<0.001	5.093 (2.072–12.521)	<0.001
Tumor grade (G3 vs. G1–2)	1.287 (0.757–2.185)	0.601	1.275 (0.725–2.243)	0.398	1.184 (0.618–2.269)	0.611	1.470 (0.618–3.495)	0.384
Hormone receptor status (positive vs. negative)	0.604 (0.368–0.991)	0.046	0.579 (0.339–0.991)	0.046	0.616 (0.330–1.149)	0.127	0.646 (0.303–1.387)	0.264
Treatment arm	1.333 (0.845–2.104)	0.216	1.453 (0.884–2.386)	0.140	1.621 (0.912–2.881)	0.099	0.873 (0.428–1.780)	0.709
Overweight/obese patients								
TILs	0.957 (0.895–1.023)	0.199	0.923 (0.849–1.003)	0.060	0.901 (0.814–0.997)	0.044	0.888 (0.781–1.009)	0.069
Menopausal status (post vs. pre)	0.798 (0.491–1.298)	0.363	0.847 (0.485–1.479)	0.560	0.819 (0.443–1.517)	0.526	1.604 (0.690–3.728)	0.272
pT stage								
pT1	Reference	0.271	Reference	0.298	Reference	0.278	Reference	0.069
pT2	1.206 (0.761–1.912)	0.424	1.404 (0.829–2.377)	0.207	1.406 (0.778–2.542)	0.259	1.688 (0.836–3.408)	0.144
pT3–4	2.179 (0.829–5.724)	0.110	1.984 (0.693–5.679)	0.201	2.250 (0.763–6.639)	0.142	4.152 (1.186–14.535)	0.026
pN stage								
pN0	Reference	0.038	Reference	0.032	Reference	0.011	Reference	0.285
pN1	1.862 (1.118–3.099)	0.017	1.626 (0.894–2.956)	0.111	2.063 (1.041–4.090)	0.038	1.535 (0.705–3.339)	0.280
pN2–3	1.832 (0.987–3.401)	0.055	2.402 (1.242–4.647)	0.009	3.075 (1.459–6.481)	0.003	1.974 (0.828–4.703)	0.125
Tumor grade (G3 vs. G1–2)	1.459 (0.860–2.475)	0.162	1.539 (0.836–2.832)	0.166	1.653 (0.835–3.274)	0.149	1.770 (0.793–3.951)	0.163
Hormone receptor status (positive vs. negative)	0.973 (0.588–1.610)	0.916	0.875 (0.501–1.528)	0.639	0.983 (0.522–1.853)	0.958	1.048 (0.496–2.211)	0.903
Treatment arm	0.950 (0.613–1.473)	0.820	1.292 (0.788–2.117)	0.310	1.343 (0.776–2.352)	0.292	1.248 (0.657–2.368)	0.499

Cox proportional hazards models were applied for DFS, RFS, DDFS, and OS, including key covariates: menopausal status, tumor size (pT), nodal stage (pN), grade, hormone receptor status, and treatment arm. TILs were analyzed as a semi-continuous variable per 5% increment. CI: confidence interval; HR: hazard ratio; OS: overall survival; TIL: tumor-infiltrating lymphocytes.

In patients who were overweight or obese, higher TIL levels were independently linked only to improved distant disease-free survival (DDFS; P=0.044), with no significant associations observed for disease-free survival (DFS; P=0.199) or recurrence-free survival (RFS; P=0.060), as detailed in **Table 1**.

This varying prognostic influence of TILs on DFS and RFS across BMI groups remained consistent in subgroup analyses stratified by hormone receptor status, age, and menopausal status.

Formal interaction testing revealed a significant interaction for RFS (P=0.044), a near-significant trend for DFS (P=0.062), and no significant interaction for DDFS (P=0.306).

We further categorized patients by TIL density using a 20% threshold to compare outcomes between high-TIL and low-TIL groups within each BMI stratum.

Among normal-weight patients, those with high TILs (≥20%) demonstrated markedly better DFS, RFS, and DDFS compared to those with low TILs (<20%), whereas overall survival (OS) showed no notable difference **(Figures 2a–2d)**. Specifically, 10-year rates for high versus low TILs were: DFS 91.3% vs. 75.9% (P=0.007), RFS 92.0% vs. 78.5% (P=0.002), DDFS

92.0% vs. 85.3% (P=0.027), and OS 92.4% vs. 90.1% (P=0.354).

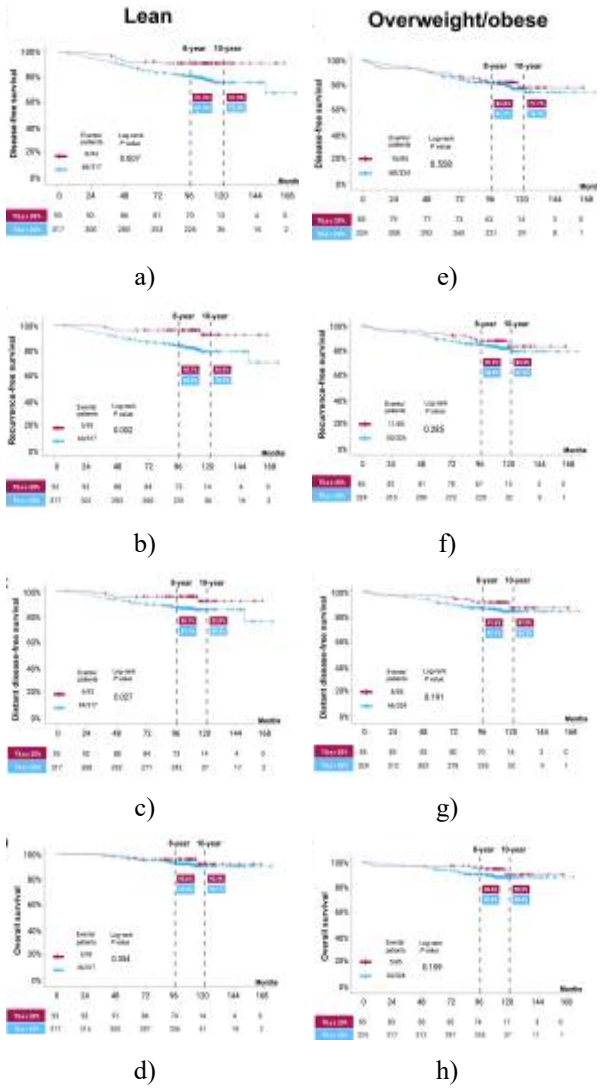

Figure 2. Kaplan–Meier plots of survival outcomes stratified by tumor-infiltrating lymphocyte levels (≥20% vs. <20%) within BMI groups. Panels (a)–(d) display results for normal-weight patients: (a) disease-free survival (DFS), (b) recurrence-free survival (RFS), (c) distant disease-free survival (DDFS), and (d) overall survival (OS). Panels (e)–(h) show corresponding outcomes for overweight/obese patients: (e) DFS, (f) RFS, (g) DDFS, and (h) OS.

Among overweight or obese patients, no meaningful differences emerged in DFS, RFS, DDFS, or OS between those with high (≥20%) and low (<20%) TILs **(Figures 2e–2h)**.

To gain deeper insight into how BMI influences TILs' prognostic value specifically in the overweight/obese subgroup—and considering that thresholds derived from normal-weight or unselected populations might not apply optimally here—we subdivided TIL levels into quartiles (0%–9%, 10%–19%, 20%–29%, and ≥30%) and compared survival across these groups **(Figure 3)**. The global log-rank tests across the four TIL categories did not reach significance for any endpoint. Specifically, 10-year rates were: DFS 74.1% (0%–9%), 86.2% (10%–19%), 91.1% (20%–29%), and 73.1% (≥30%; P=0.118); RFS 78.9%, 91.7%, 91.1%, and 80.6% (P=0.103); DDFS 81.8%, 93.1%, 91.1%, and 85.7% (P=0.127); and OS 87.0%, 93.6%, 95.7%, and 88.9% (P=0.196).

Visual review of the curves suggested separation, with the lowest TIL group (0%–9%) faring worse than the others, particularly for RFS, DDFS, and OS. A subsequent Cox model comparing <10% vs. ≥10% TILs confirmed this pattern: patients with very low TILs (<10%) showed inferior outcomes (DFS: HR 0.64, 95% CI 0.40–1.03, P=0.066; RFS: HR 0.52, 95% CI 0.30–0.90, P=0.021; DDFS: HR 0.48, 95% CI 0.26–0.89, P=0.021; OS: HR 0.45, 95% CI 0.21–0.95, P=0.036).

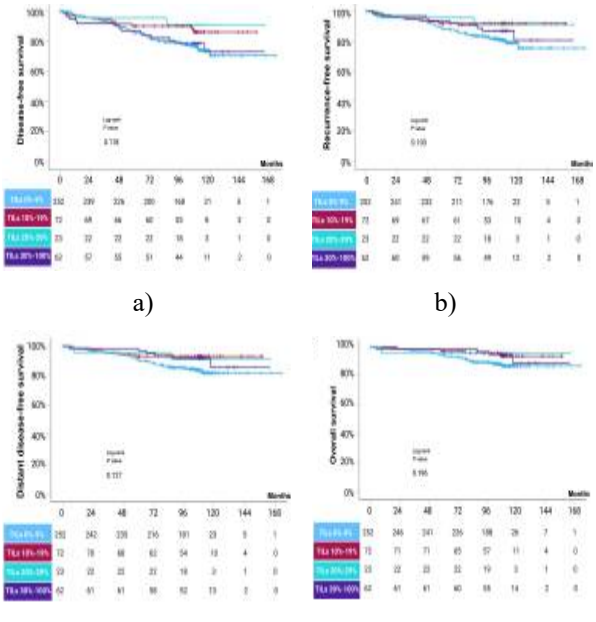

Figure 3. Kaplan–Meier survival estimates for overweight and obese patients, stratified by finer TIL categories (0%–9%, 10%–19%, 20%–29%, and ≥30%). Panels show: (a) disease-free survival (DFS), (b) recurrence-free survival (RFS), (c) distant disease-free survival (DDFS), and (d) overall survival (OS).

Competing risks analysis

Eight-year cumulative incidence rates for different types of first events, stratified by BMI category and TIL levels, are presented in **Figure 4**.

Group		N pts	Locoregional relapse		Distant relapse		Second primary cancer		Death	
BMI	TILs		8-yr %	p	8-yr %	p	8-yr %	p	8-yr %	p
Lean	<10%	251	5.2%	0.06	10.6%	0.03	3.3%	0.92	0.4%	0.74
	≥10%	159	2.6%		5.1%		3.9%		0.6%	
	<20%	317	5.4%	0.01	9.6%	0.07	3.2%	0.81	0.6%	0.44
	≥20%	93	0.0%		4.3%		4.4%		0.0%	
Overweight/ obese	<10%	252	2.8%	0.79	10.1%	0.01	4.8%	0.86	2.5%	0.8
	≥10%	157	3.2%		3.9%		3.8%		3.3%	
	<20%	324	2.6%	0.54	8.7%	0.05	4.4%	0.91	2.2%	0.31
	≥20%	85	4.8%		3.6%		4.7%		4.8%	

Figure 4. Competing risk analysis displaying the 8-year cumulative incidence of different initial recurrence types, categorized according to body mass index (BMI) and tumor-infiltrating lymphocyte (TIL) levels.

Among patients with normal weight (lean), those with lower TIL levels showed elevated rates of locoregional recurrence (with statistical significance) and a trend toward higher distant recurrence (though not reaching significance) relative to patients with higher TILs.

In contrast, among patients classified as overweight or obese, lower TIL levels were linked to a markedly increased rate of distant recurrence (statistically significant), while rates of other recurrence types showed no notable differences.

For cases where locoregional recurrence occurred first [22 events in the lean group (all 22 with low TILs, none with high TILs); 14 events in the overweight/obese group (10 with low TILs, 4 with high TILs)], breast-conserving surgery was performed in 59.1% of lean cases and 64% of overweight/obese cases. Furthermore, no significant variations in locoregional management approaches (including radiotherapy or surgical method) emerged between high- and low-TIL groups within different BMI strata.

This exploratory evaluation within the ShortHER trial explored how BMI influences the prognostic significance of TILs in early-stage HER2-positive breast cancer. The data suggest that elevated BMI could diminish the beneficial role of TILs, especially regarding protection from locoregional recurrences in individuals with overweight or obesity.

Specifically, TILs demonstrated a robust, independent association with improved outcomes in lean patients across multiple measures, including disease-free survival (DFS), relapse-free survival (RFS), and distant disease-free survival (DDFS). However, in the overweight/obese cohort, this association persisted significantly only for DDFS. A significant interaction term between TILs (analyzed per 5% increase) and BMI was detected for RFS (with borderline significance for DFS), but absent for DDFS, reinforcing this pattern.

Additional investigations in the overweight/obese subgroup involved dividing patients into four TIL quartiles for survival comparisons. These revealed a threshold effect: a TIL level of at least 10% identified distinct prognostic subgroups, yet further elevations in TILs beyond this point did not yield additional prognostic gains.

These observations, to the best of our knowledge, offer the initial clinical support for adiposity potentially exerting an immunomodulatory influence that alters TILs' prognostic value in HER2-positive breast cancer [10, 24]. The analysis drew from what remains the strongest evidence base confirming TILs' importance for DDFS and overall survival in this subtype.

In distinction from results reported in other randomized trials [18-20], BMI did not emerge here as an independent prognostic determinant in HER2-positive patients receiving combined chemotherapy and anti-HER2 treatment. As a continuous measure, BMI correlated with overall survival (indicating a 4% rise in mortality risk per unit increase), but lacked parallel ties to more breast-cancer-specific measures like DFS, RFS, or DDFS. This pattern probably underscores the known broader influence of higher BMI on general mortality rather than a direct impact on cancer progression in this treated population.

That said, the findings resonate with a planned subgroup evaluation from the Aphinity trial [18], where elevated BMI worsened prognosis under dual HER2 inhibition (trastuzumab plus pertuzumab), yet showed no such effect in the single-agent trastuzumab arm (with placebo), featuring comparable hazard ratios and event frequencies irrespective of BMI.

Emerging preliminary evidence supports speculation about a multifaceted interaction involving adiposity, HER2-driven oncogenic pathways, and potential resistance to anti-HER2 therapies [30-32], where the

chronic low-grade inflammation associated with obesity might compromise antitumor immune responses [21].

When extending the comparison to other breast cancer subtypes, our results align with earlier studies in triple-negative breast cancer patients receiving neoadjuvant chemotherapy [33], which indicated that elevated TIL levels were associated with improved event-free survival primarily in lean individuals, but not in those with overweight or obesity. However, the absence of detailed breakdown by event type (local versus distant) in that prior work limits direct parallels with our observations on differential effects across relapse sites.

This study enhances the biological credibility of the idea that obesity could compromise immune function within the tumor's local microenvironment by promoting an immunosuppressive phenotype—a concept previously proposed based on evidence of obesity-linked T-cell impairment in various cancers [21]. The observed threshold-like relationship between TIL levels and outcomes in overweight/obese patients might indicate that higher TIL densities increasingly include exhausted or regulatory immune cells, underscoring the intricate nature of this interaction.

Taken together, the accumulating evidence—including contributions from our work—questions the reliability of TILs as a consistent prognostic marker in early breast cancer patients with overweight or obesity. However, our data temper this concern by showing that the diminished protective role of TILs appears confined to locoregional recurrences, while reassuringly preserved for distant metastases—the event with the greatest clinical consequence for patients. Competing risk analyses corroborated this, demonstrating reduced rates of distant relapse as the initial event among patients with high TILs versus low TILs, irrespective of BMI category (both in lean and overweight/obese groups).

In exploring potential explanations for this site-specific difference, we noted that most patients with locoregional recurrence as their first event had received breast-conserving surgery. Given the higher frequency of this surgical approach in the overweight/obese subgroup compared to lean patients, the remaining breast tissue might exacerbate adiposity-related local immunosuppression, thereby counteracting TILs' usual protective effect against local failure. That said, the small number of locoregional events warrants interpretive caution; these patterns could stem from insufficient statistical power rather than a genuine biological mechanism.

A primary limitation of this analysis is the reliance on BMI measured at trial randomization. While BMI serves as a convenient proxy for adiposity and nutritional status, it has inherent shortcomings: it fails to capture body composition, fat distribution, or nuances in certain demographics (e.g., muscular individuals or older adults). Moreover, a single baseline assessment overlooks potential changes in weight or nutritional status during or following adjuvant therapy—including endocrine treatment in hormone receptor-positive cases—yielding an incomplete longitudinal view. Existing data on the prognostic implications of weight fluctuations during adjuvant therapy in HER2-positive breast cancer remain inconsistent, with some studies identifying adverse effects [19] and others finding none [18].

Another key limitation arises from using overall TIL density without detailed characterization of immune cell subsets. It is plausible that the tumor microenvironment in overweight/obese patients features a greater proportion of suppressive immune elements relative to lean patients, which could undermine the typical benefits linked to high TIL infiltration in HER2-positive disease [1-10].

Further constraints include the analysis cohort representing only 65% of the full ShortHER trial population (albeit demographically similar) and the exploratory, post-hoc design of the investigations.

Conclusion

In summary, our results indicate that elevated BMI may selectively diminish the protective influence of TILs against locoregional—but not distant—recurrences in overweight or obese patients with early HER2-positive breast cancer receiving adjuvant chemotherapy plus trastuzumab. To our knowledge, this represents the first such evidence in HER2-positive disease, derived from the most robust dataset affirming TILs' prognostic value in this subtype. Amid the worldwide obesity epidemic, [34] and considering that over half of patients in our ShortHER BMI cohort had overweight or obesity, prioritizing research to unravel the interactions among immunity, HER2 signaling, targeted therapies, and adiposity in obese individuals is essential. These insights apply not to a marginal subset, but to a significant segment of patients undergoing curative-intent treatment for HER2-positive breast cancer.

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