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ORIGINAL ARTICLE

Interaction between tumor-infiltrating lymphocytes and BMI in early HER2-positive breast cancer: analysis of the ShortHER trial☆

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Background: We demonstrated the prognostic role of tumor-infiltrating lymphocytes (TILs) in patients with early human epidermal growth factor receptor 2 (HER2)-positive breast cancer (eBC) enrolled in the ShortHER trial. Here, we analyze how body mass index (BMI) modulates the prognostic role of TILs.
Patients and methods: The ShortHER study randomized 1253 patients with HER2-positive eBC to 9 weeks versus 1 year of adjuvant trastuzumab + chemotherapy. We assessed BMI at diagnosis (available for $n = 1213$, $n = 34$ underweight were excluded). Survival endpoints were disease-free survival (DFS), recurrence-free survival (RFS), distant DFS (DDFS) and overall survival (OS). We calculated the cumulative incidence of first event types by competing risk analysis.
Results: A total of 583 (48%) patients were lean, 360 (29.7%) overweight and 236 (19.5%) obese. Lean patients versus those with overweight or obesity had similar DFS, RFS, DDFS and OS. Within the TIL + BMI cohort ($n = 819$), TILs (5% increase) were independently associated with DFS ($P = 0.003$), RFS ($P = 0.001$) and DDFS ($P = 0.018$) in lean patients. In patients with overweight or obesity, TILs were independently associated only with DDFS ($P = 0.044$). In lean patients, TILs ≥20% were associated with improved DFS ($P = 0.007$), RFS ($P = 0.002$) and DDFS ($P = 0.027$) compared with TILs <20%. In patients with overweight or obesity, DFS, RFS, DDFS and OS did not significantly differ between TILs ≥20% and TILs <20%. In lean patients, there was a higher cumulative incidence of locoregional relapse ($P = 0.001$) and distant relapse ($P = 0.07$) in patients with TILs <20% versus TILs ≥20%. In patients with overweight or obesity, there was a higher cumulative incidence of distant relapse ($P = 0.005$) in patients with TILs <20% versus TILs ≥20%.
Conclusions: We suggest that BMI may impair the local, but not distant, protective effect of TILs in patients with overweight or obesity with HER2-positive eBC treated with adjuvant chemotherapy + trastuzumab.
Keywords: breast cancer, HER2-positive, TILs, BMI

INTRODUCTION

In the past decades, we have witnessed a progressive optimization of the therapeutic approach for treating patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC), leading to unprecedented curability rates. However, a substantial degree of prognostic heterogeneity—not fully captured by established prognostic factors—still exists, thus mandating a continued effort to refine our understanding of this

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complexity. Within this framework, tumor-infiltrating lymphocytes (TILs) have emerged as a promising biomarker capable of enhancing our prognostication abilities, as they have been consistently shown to predict survival outcomes in HER2-positive early BC patients receiving chemotherapy + anti-HER2-based systemic treatment in the curative setting.[1-9]

The ShortHER trial was a phase III randomized trial designed to test the non-inferiority of 9 weeks (short arm) versus 1 year (long arm) of adjuvant trastuzumab in patients with HER2-positive early BC. Within this trial, we provided the demonstration of a strong independent prognostic role of TILs and also suggest a potential interaction between the TILs and treatment, with patients with high TILs (≥20%) not experiencing any detrimental impact on the risk of distant relapse or death when treated with the de-escalated regimen.[10]

Adiposity is a well-established risk factor for the development of BC, particularly in the postmenopausal phase,[11,12] primarily driven by increased aromatization of androgens into estrogens and the promotion of a low-grade chronic inflammation, both mediated by the greater abundance of adipose tissue. Moreover, obese women diagnosed with BC are exposed to an excess risk of recurrence and death as compared with lean patients.[13-16] This has been robustly demonstrated for hormone receptor-positive/HER2-negative BC, and data are also accumulating for HER2-positive disease.[17-20]

Although it has been hypothesized that altered inflammation, impaired antitumor immune responses and changes in the tumor microenvironment[16,21] may substantially contribute to such detrimental impact of obesity in patients diagnosed with BC, we currently lack tools to adequately measure these phenomena and estimate their clinical impact.

Here, we explore how body adiposity—surrogated by body mass index (BMI)—can modulate the prognostic impact of TILs, by leveraging the ShortHER trial as a clinical platform.

PATIENTS AND METHODS

Study population

The ShortHER trial (EudraCT: 2007-004326-25; ClinicalTrials.gov Identifier: NCT00629278) was a multicenter phase III randomized non-inferiority trial conducted in Italy. Details regarding study design, participants, procedures and the statistical implant have been detailed elsewhere[22,23] (protocol in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105832).

In brief, 1254 patients with surgically resected HER2-positive BC were randomized to receive either 9 weeks (short arm, $n = 627$) or 1 year (long arm, $n = 627$) of adjuvant trastuzumab in combination with chemotherapy. The chemotherapy regimen also differed between treatment arms consisting of adriamycin-cyclophosphamide/epidoxorubicin-cyclophosphamide once every 3 weeks for four courses followed by paclitaxel/docetaxel once every 3 weeks for four courses in the long arm versus docetaxel once every 3 weeks for three courses followed by 5-fluorouracil-epidoxorubicin-cyclophosphamide once every 3 weeks for three courses. At the end of chemotherapy, radiotherapy and hormonal therapy were carried out, when indicated, according to local standard. Analysis of the primary endpoint disease-free survival (DFS) failed to formally establish the non-inferiority of the short arm versus the long arm.[22] However, at the most recent update, 10-year estimates for DFS and overall survival (OS) were almost superimposable between the two arms.[23]

Within the ShortHER cohort, 893 patients were suitable for TIL assessment ($n = 441$ in the long arm, $n = 452$ in the short arm). An initial analysis at a median follow-up of 6 years showed a significant prognostic impact of TILs on distant disease-free survival (DDFS).[24] These data were confirmed at a later follow-up (median 9 years) analysis, which also demonstrated for the first time a prognostic effect of TILs on OS for patients with early HER2-positive BC. Indeed, each 5% increment of TIL levels was associated with both DDFS and OS improvement [DDFS: hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.80-0.95, $P = 0.001$; OS: HR 0.89, 95% CI 0.81-0.98, $P = 0.01$].[10]

The ShortHER trial was approved by local ethical committees and conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients provided written informed consent for tumor sample use for research purposes. The trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

For the present exploratory analyses, the BMI cohort included all patients with available BMI data at randomization, excluding those with underweight, while the BMI-TIL cohort comprised patients with both BMI (excluding underweight) and TIL data available. The rationale for excluding underweight patients, together with the corresponding numbers, is detailed in the 'Biomarker assessment' and 'Statistical analysis' sections, and the overall selection process is visually depicted in the study workflow (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105832).

Biomarker assessment

HER2 and hormone receptor status were assessed locally. Hormone receptor-positive status was defined as estrogen receptor and/or progesterone receptor expression ≥10%.

BMI was assessed at randomization and defined as a patient's weight in kilograms divided by the square of the patient's height in meters (kg/m^2). According to BMI ranges endorsed by the World Health Organization, patients were categorized as follows: underweight (BMI <18.5 kg/m^2), lean (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), obese (BMI ≥30 kg/m^2).

TILs were centrally scored on primary tumor tissue, evaluating a single hematoxylin—eosin-stained slide, by complying with the guideline recommendations for TIL assessment.[25] Details on the TIL assessment, including concordance between the two investigators (MVD and MS) involved in scoring, have been previously reported.[10]

Statistical analysis

Since the population for the BMI analysis was based on the total number of patients with BMI available at the time of randomization ($n = 1213/1253$), no formal sample size calculation was carried out.

Survival endpoints for this analysis were as follows: DFS, defined as the time from randomization to second primary cancer, locoregional relapse, distant relapse or death; RFS, defined as the time from randomization to locoregional relapse, distant relapse or death; DDFS, defined as the time from randomization to distant relapse or death; OS, defined as the time from randomization to death.

For the purposes of this analysis, underweight patients ($n = 34$ in the BMI cohort and $n = 21$ in the BMI-TIL cohort) were excluded, given their low proportion and expected adverse prognosis.[26,27]

For survival analysis according to BMI, patients were divided into two groups: lean versus overweight/obese.

For the assessment of the prognostic role of TILs across BMI categories, we used the Cox regression model to calculate HR and 95% CI by considering TILs as a semi-continuous variable (5% increment), and the Kaplan—Meier method to estimate survival curves by considering TILs as a categorical variable (20% cut-off). The 20% cut-off was chosen for reasons of consistency with previously published analyses,[10,24] where it had been originally defined to identify a subgroup of patients with an estimated 5-year DDFS rate of at least 95%, regarded as a clinically acceptable definition of low-risk disease. Guided by the observations that emerged during the analyses, we also explored alternative categorizations, with a particular focus on the subgroup of patients with overweight/obesity.

A competing risk methodology[28,29] was adopted to evaluate the cumulative incidence of first events. The following events were considered as competing risks: locoregional relapse, distant relapse, second primary cancer, death without any other prior event. Patients who had not experienced any of the competing risk events at the last follow-up date were censored at that time. Patients who experienced concomitant locoregional and distant relapses as first events were considered to have distant relapse as their first event.

Statistical analyses were carried out using SPSS, version 29 (IBM Corp., Armonk, NY). All tests were two-sided, and statistical significance was set at $P < 0.05$.

RESULTS

Patients' characteristics and prognostic impact of BMI in the BMI cohort

The 'BMI cohort' included 1179 patients with BMI data available at the time of randomization and BMI >18.5 kg/m^2 (94.1% of all patients randomized in the ShortHER trial), as shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105832. A total of 583 patients (49.4%) were lean, 360 (30.6%) overweight and 236 (20.0%) obese.

Clinicopathological features of the BMI cohorts are shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105832.

The group with overweight or obesity, as compared with lean patients, was enriched for: older and postmenopausal women, tumors with higher pathological stages (pT and pN) and hormone receptor positivity. In addition, patients with overweight or obesity underwent significantly higher rates of conservative breast surgery, as compared with their lean counterparts.

BMI was not significantly associated with survival endpoints. In particular, compared with patients with overweight or obesity, the lean subgroup experienced similar DFS (10-year DFS 78.6% versus 76.6%, $P = 0.484$), RFS (10-year RFS 81.5% versus 81.3%, $P = 0.765$), DDFS (10-year DDFS 86.3% versus 84.3%, $P = 0.465$) and OS (10-year OS 90.4% versus 88.0%, $P = 0.151$), as shown in Figure 1A-D. Consistently, no statistically significant association was observed between BMI as a continuous variable and DFS, RFS and DDFS. Conversely, a significant association was observed between BMI (continuous) and OS [univariate analysis, DFS: HR 1.01, 95% CI 0.99-1.04, $P = 0.360$; RFS: HR 1.01, 95% CI 0.98-1.04, $P = 0.570$; distant RFS (DRFS): HR 1.02, 95% CI 0.99-1.05, $P = 0.230$; OS: HR 1.04, 95% CI 1.00-1.07, $P = 0.041$] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105832).

In Cox models including relevant variables (menopausal status, pT, pN, tumor grade, hormone receptor status, treatment arm), no survival differences were detected between lean patients and those with overweight or obesity, as shown in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105832.

BMI + TIL cohort: association of TILs with prognosis according to BMI

The 'BMI + TIL cohort' included 819 patients from the BMI cohort with available TIL data, as summarized in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105832.

The BMI + TIL cohort was representative of the overall ShortHER cohort, with the only exception represented by slightly older age and slightly lower TILs in the BMI-TIL cohort as compared with the overall ShortHER cohort (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105832).

BMI categories were as follows: lean (410, 50.1%), overweight (246, 30.0%) and obese (163, 19.9%).

In adjusted Cox models (Table 1), in lean patients, there was a statistically significant association between TILs as a semi-continuous variable (5% increment) and DFS ($P = 0.003$), RFS ($P = 0.001$) and DDFS ($P = 0.019$), as shown in Table 1.

For patients with overweight or obesity, TILs were significantly associated only with DDFS ($P = 0.044$), and not with DFS ($P = 0.199$) and RFS ($P = 0.060$), as shown in Table 1.

The differential prognostic impact of TILs on DFS and RFS according to BMI category was confirmed at the analysis stratified per hormone receptor status, age and menopausal

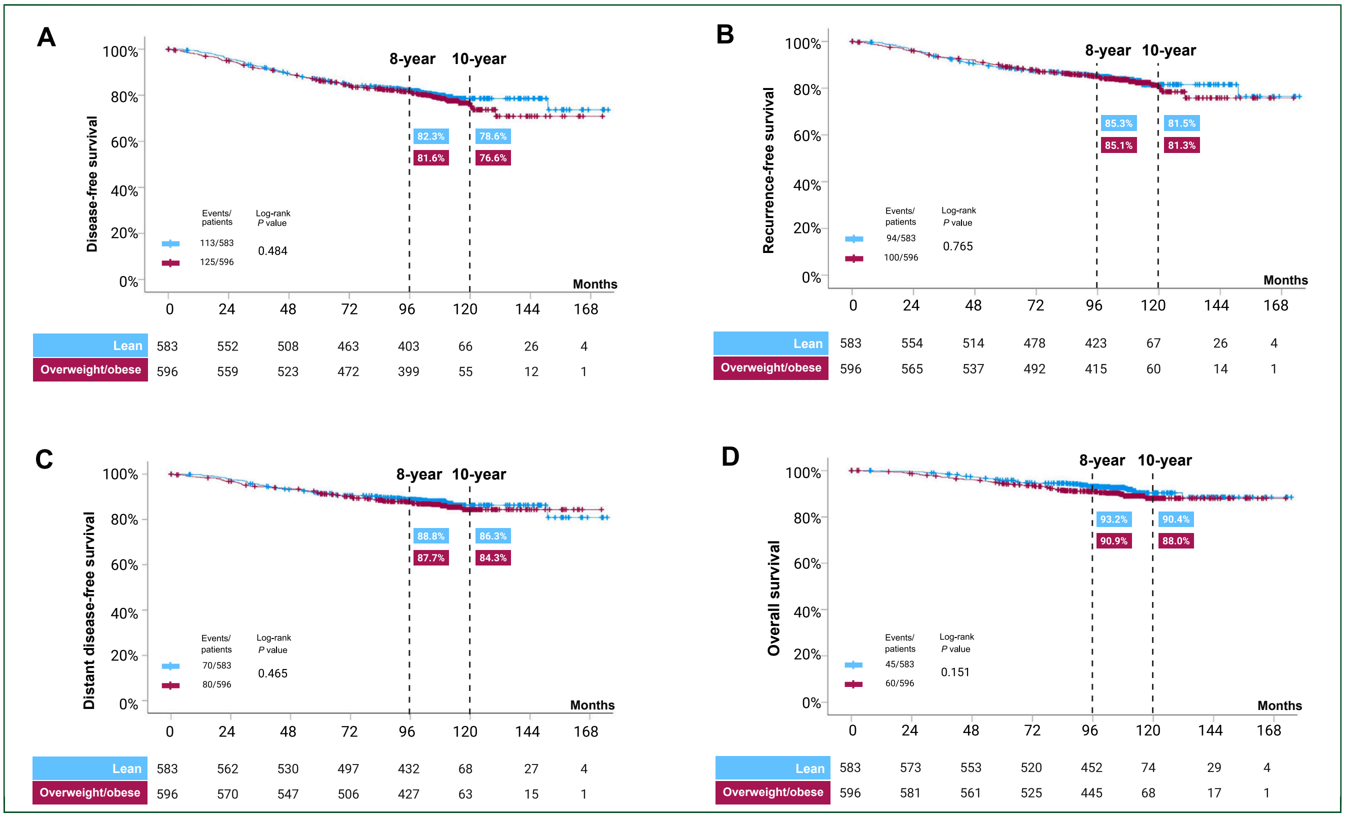

Figure 1. Kaplan Meier curves according to BMI categories (lean versus overweight/obese). (A) disease-free survival (DFS), (B) recurrence-free survival (RFS), (C) distant disease-free survival (DDFS) and (D) overall survival (OS).

status, as shown in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105832.

Interaction test was statistically significant for RFS (P = 0.044), borderline—not statistically—significant for DFS (P = 0.062) and not significant for DDFS (P = 0.306).

We then stratified patients according to TIL levels, comparing survival curves between those with high and low TILs (20% cut-off) across BMI categories.

In the lean subgroup, patients with high TILs experienced significantly longer DFS, RFS and DDFS as compared with those with low TILs, while no significant difference was observed for OS, as shown in Figure 2A-D. In particular, comparing high versus low TILs, 10-year DFS was 91.3% versus 75.9% (P = 0.007), 10-year RFS was 92.0% versus 78.5% (P = 0.002), 10-year DDFS was 92.0% versus 85.3% (P = 0.027) and 10-year OS was 92.4% versus 90.1% (P = 0.354).

In the subgroup with overweight or obesity, DFS, RFS, DDFS and OS did not significantly differ between high and low TILs, as shown in Figure 2E-H.

To further explore the role of BMI in modulating the prognostic role of TILs among patients with overweight/obesity, and based on the hypothesis that TIL cut-offs established as prognostic in lean or unselected BC populations may be suboptimally informative in this subgroup, we compared survival curves across four categories defined by TILs 0%-9% versus 10%-19% versus 20%-29% versus 30%-100%, as shown in Figure 3. The overall log-rank test comparing the four categories was not significant for any of the survival endpoint. In particular, for TILs 0%-9% versus 10%-19% versus 20%-29% versus 30%-100%, 10-year DFS was 74.1% versus 86.2% versus 91.1% versus 73.1%, P = 0.118; 10-year RFS was 78.9% versus 91.7% versus 91.1% versus 80.6%, P = 0.103; 10-year DDFS was 81.8% versus 93.1% versus 91.1% versus 85.7%, P = 0.127; and 10-year OS was 87.0% versus 93.6% versus 95.7% versus 88.9%, P = 0.196. By visual inspection of the curves, we observed a separation between the 0%-9% group and the other categories especially for RFS, DDFS and OS. Thus, we built a Cox model to further investigate this finding, showing that patients with $<$10% of TILs had poorer outcomes than those with TILs $\geq$10% (TILs $<$10% versus $\geq$10%: 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).

Competing risk analysis

The 8-year cumulative incidence rates of first event types by BMI and TILs are reported in Figure 4.

In the lean subgroup, there was a higher cumulative incidence of locoregional relapse (statistically significant) and distant relapse (not statistically significant) in patients with low TILs compared with those with high TILs.

In the subgroup with overweight or obesity, we found a significantly higher cumulative incidence of distant relapse in patients with low TILs compared with those with high TILs, with no difference in incidence of other types of events.

Table 1. Multivariate survival analysis according to TILs in lean patients and in those with overweight/obesity

	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								
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 versus 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								
pT1	Ref.	0.212	Ref.	0.127	Ref.	0.060	Ref.	0.206
pT2	1.542 (0.945-2.516)	0.083	0.176 (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								
pN0	Ref.	0.075	Ref.	0.048	Ref.	0.001	Ref.	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)	0.46	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
Grade (G3 versus 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 versus 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/obesity								
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 versus 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								
pT1	Ref.	0.271	Ref.	0.298	Ref.	0.278	Ref.	0.069
pT2	1.206 (0.761-1.912)	0.424	1.404 (0.829-2.377)	0.207	0.1406 (0.778-2.542)	0.259	1.688 (0.836-3.408)	0.144
pT3-4	2.179 (0.829-5.724)	0.11	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								
pN0	Ref.	0.038	Ref.	0.032	Ref.	0.011	Ref.	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
Grade (G3 versus 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 versus 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 models for disease-free survival (DFS), recurrence-free survival (RFS) and distant disease-free survival (DDFS), including relevant variables (menopausal status, pT, pN, tumor grade, hormone receptor status, treatment arm), according to TILs as a semicontinuous variable (5% increment).
CI, confidence interval; HR, hazard ratio; OS, overall survival; TIL, tumor-infiltrating lymphocyte.

Among patients with a locoregional relapse as the first event [$n = 22$ in the lean subgroup ($n = 22$ low TILs, $n = 0$ high TILs); $n = 14$ in the subgroup with overweight or obesity ($n = 10$ low TILs, $n = 4$ high TILs)], 59.1% of lean patients and 64% of obese patients underwent breast-conserving surgery. The distribution of TIL levels in patients with locoregional relapse and conservative surgery is shown in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105832. Moreover, no statistically significant difference in terms of locoregional treatments (radiotherapy and type of surgery) was observed in high versus low TILs across BMI categories, as shown in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105832.

DISCUSSION

In this exploratory analysis of the ShortHER trial, we investigated the interplay between BMI and the prognostic role of TILs in HER2-positive early BC. We suggested that BMI may negatively modulate the protective impact of TILs, with respect to local relapses in patients with overweight or obesity. In particular, we observed that, while in lean women TILs retained a significant and independent prognostic impact in terms of both DFS/RFS and DDFS, in patients with overweight or obesity TILs significantly predicted only DDFS. This observation was further strengthened by the statistically significant interaction between TILs (5% increment) and BMI found only for RFS (borderline significant for DFS), but not for DDFS. Building on these results, we further investigated the modulatory role of BMI in shaping the prognostic impact of TILs among patients with overweight/obesity. In exploratory analyses, survival curves were compared across four TIL categories. This allowed us to uncover a non-linear association between TILs and outcome in patients with overweight/obesity. Indeed, a $\geq$10% cut-off was able to discriminate two groups of patients with different prognosis. However, increasing TIL levels were not further linked to progressively better outcomes.

To our knowledge, these results provide the first clinical evidence of a potential immunomodulatory effect of adiposity on the prognostic role of TILs in HER2-positive BC. Notably, this analysis was conducted within the most robust study to date establishing the prognostic relevance of TILs for DDFS and OS in the HER2-positive setting.[10,24] As opposed to other previous findings generated within randomized clinical trial platforms,[18-20] we did not observe a

Figure 2. Kaplan—Meier curves for tumor-infiltrating lymphocytes (TILs) (≥20% versus <20%) across body mass index (BMI) categories. (A) Disease-free survival (DFS) for lean; (B) recurrence-free survival (RFS) for lean; (C) distant disease-free survival (DDFS) for lean; (D) overall survival (OS) for lean; (E) DFS for overweight/obese; (F) RFS for overweight/obese; (G) DDFS for overweight/obese; (H) OS for overweight/obese.

direct prognostic role of BMI as a stand-alone factor in patients with HER2-positive BC receiving chemotherapy + anti-HER2 blockade. When modeled as a continuous variable, BMI showed an association with OS (4% increased mortality per BMI unit) without consistent associations across endpoints more specific to BC events (DFS, RFS, DDFS). This isolated finding is more likely to reflect the broader and well-recognized adverse effect of higher BMI on all-cause mortality, rather than a BC-specific prognostic effect in this specific patient population. Nonetheless, our results well align with a predefined subgroup analysis within the Aphinity trial,[18] showing that while BMI retained a negative prognostic role in patients receiving dual HER2 blockade with trastuzumab and pertuzumab, it did not

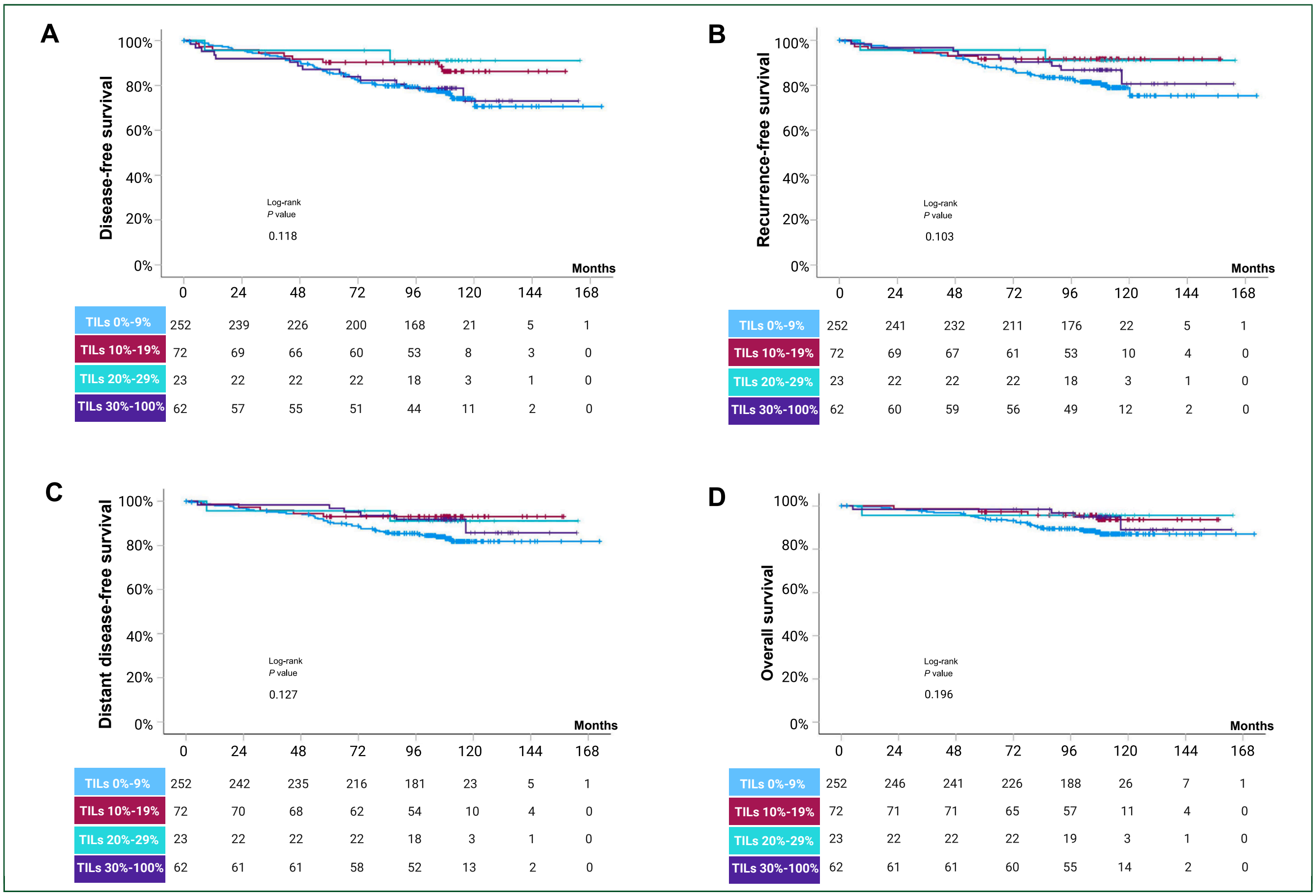

Figure 3. Kaplan—Meier curves for tumor-infiltrating lymphocytes (TILs) (0%-9% versus 10%-19% versus 20%-29% versus 30%-100%) in patients with overweight/obesity. (A) Disease-free survival (DFS); (B) recurrence-free survival (RFS); (C) distant disease-free survival (DDFS); (D) overall survival (OS).

affect invasive DFS, DRFS and OS in those receiving single HER2 blockade with trastuzumab (plus placebo), with similar adjusted HR and event rates across BMI categories.

A growing body of preliminary data allows to speculate on a more complex interplay between adiposity, the HER2 oncogenic signaling and resistance to HER2 pharmacological blockade,[30-32] whereby the obesity-induced meta-inflammatory state may impair antitumor immunity.[21]

When broadening the perspective to include other BC subtypes, our findings appear in line with previous reports suggesting that BMI can modify the prognostic role of TILs in patients with triple-negative BC treated with neoadjuvant chemotherapy,[33] where high TIL levels predicted

Group: BMI	Group: TILs	N pts	Locoregional relapse: 8-yr %	Locoregional relapse: p	Distant relapse: 8-yr %	Distant relapse: p	Second primary cancer: 8-yr %	Second primary cancer: p	Death: 8-yr %	Death: 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 with 8-year cumulative incidence rates of first event types by body mass index (BMI) and tumor-infiltrating lymphocytes (TILs).

longer event-free survival in lean patients but not in those with overweight or obesity. However, the lack of granular data regarding the type of event-free survival event in this previous report precludes the possibility of appraising the differential prognostic impact of TILs in terms of local versus distant relapse, thus making the comparison with our results incompletely informative.

Our study contributes to increasing the biological plausibility of the hypothesis that obesity may disrupt the immune competence at the level of local microenvironment, by polarizing it toward immunosuppression, as already postulated based on the observation of obesity-related T-cell dysfunction across multiple tumor types.[21] The non-linear association between TIL levels and prognosis identified in patients with overweight/obesity may reflect a progressive enrichment of the infiltrate with exhausted and/or immunosuppressive lymphocytes as TIL density increases, further highlighting the complexity of this interplay.

Overall, while the available evidence, to which our study adds, raises concerns regarding the validity of TILs as a reliable prognostic biomarker in patients with overweight or obesity with early BC, our findings may resize the proportion of this alert by suggesting a lack of protective effect of TILs only for local relapse, and, reassuringly, not for distant relapse, which represents the most transformative and impactful event for patients with a BC diagnosis. The preserved protective effect of TILs for distant relapse irrespectively from BMI was further confirmed at the competing risk analysis, revealing a lower incidence of distant relapse as the first event in patients with high TILs as compared with those with low TILs, both in lean women and those with overweight or obesity. On the other hand, when trying to elucidate such differential prognostic effect, we observed that, among patients experiencing local relapse as the first event, the majority of them underwent breast-conserving surgery. Since patients with obesity were more often treated with breast-conserving surgery compared with lean ones, the residual breast tissue may have amplified the local immunosuppressive effect of adiposity in this patient population, potentially neutralizing the protective role of TILs against local relapses. Of course, the low absolute number of local events imposes caution in the interpretation of these findings and precludes the possibility to draw definitive conclusions in this regard, as this observation may simply reflect limited statistical power rather than a true biological difference.

The adoption, for the purposes of this analysis, of BMI data at randomization represents the main limitation, with implications at several levels. Firstly, although BMI is the most practical surrogate for assessing body adiposity and nutritional status, it is an imperfect measure: it does not account for body composition or fat distribution and may be misleading in specific populations, such as athletes and the elderly. In addition, although baseline BMI well reflects the nutritional status at diagnosis, it misses the possible nutritional status modification while on and after the exposure to adjuvant treatment—including hormonal therapy for the hormone receptor-positive subgroup—thus unavoidably providing an incomplete picture. Evidence regarding the prognostic impact of BMI changes during adjuvant treatment in patients with HER2-positive BC is conflicting, with reports supporting a negative role[19] and others failing to capture such an association.[18]

Given the emerging immunomodulatory role of BMI, the use of a crude assessment of TIL levels without granular data regarding the composition of the tumor immune infiltrate represents another limitation. It is indeed reasonable to speculate that the breast microenvironment of patients with overweight or obesity may harbor a heavier representation of immune cells with immunosuppressive polarization compared with their lean counterparts, potentially impairing the protective effect typically associated with TIL abundance in HER2-positive BC.[1-10]

Additional limitations include the restriction of the BMI + TIL cohort to 65% of the ShortHER population, although broadly representative of the original trial population, and the retrospective, non-prespecified nature of the analyses.

In conclusion, our findings suggest that BMI may impair the local, but not distant, protective effect of TILs in patients with overweight or obesity with HER2-positive early BC treated with adjuvant chemotherapy and trastuzumab. To our knowledge, these are the first data of this kind in HER2-positive disease, and they stem from the most solid study to date on the prognostic role of TILs in this specific subtype. Given the global obesity burden,[34] and the observation that more than half of the patients in the ShortHER BMI cohort were overweight or obese, the generation of data capable of elucidating the complex interplay between immunity, HER2-positive cancer cells and treatments in obese patients should be considered a research priority. This emphasizes that the considerations raised for patients with overweight/obesity do not pertain to a niche subgroup, but rather to a substantial proportion of the HER2-positive BC population treated in the curative setting.

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