European Journal of Cancer 191 (2023) 112988

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Association of body mass index with clinicopathological features and survival in patients with primary invasive lobular breast cancer☆

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Received 11 April 2023; Received in revised form 29 June 2023; Accepted 5 July 2023
Available online 13 July 2023

☆ Abstract presented as a poster presentation at SABCS 2022.

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https://doi.org/10.1016/j.ejca.2023.112988

KEYWORDS
Invasive lobular breast cancer;
Body mass index;
Obesity;
Clinicopathological features;
Survival analyses

Abstract ***Purpose:*** Invasive lobular carcinoma (ILC) represents up to 15% of all breast carcinomas. While the proportion of women with overweight and obesity increases globally, the impact of body mass index (BMI) at primary diagnosis on clinicopathological features of ILC and the prognosis of the patients has not been investigated yet.

Patients and methods: We performed a multicentric retrospective study including patients diagnosed with non-metastatic pure ILC. The association of BMI at diagnosis with clinicopathological variables was assessed using linear or multinomial logistic regression. Univariable and multivariable survival analyses were performed to evaluate the association of BMI with disease-free survival (DFS), distant recurrence-free survival (DRFS), and overall survival (OS).

Results: The data of 2856 patients with ILC and available BMI at diagnosis were collected, of which 2570/2856 (90.0%) had oestrogen receptor (ER)-positive and human epidermal growth factor receptor (HER2) not amplified/overexpressed (ER+/HER2−) ILC. Of these 2570 patients, 80 were underweight (3.1%), 1410 were lean (54.9%), 712 were overweight (27.7%), and 368 were obese (14.3%). Older age at diagnosis, a higher tumour grade, a larger tumour size, a nodal involvement, and multifocality were associated with a higher BMI. In univariable models, higher BMI was associated with worse outcomes for all end-points (DFS: hazard ratio (HR) 1.21, 95CI 1.12–1.31, p value < 0.01; DRFS: HR 1.25, 95CI 1.12–1.40, p value < 0.01; OS: HR 1.25, 95CI 1.13–1.37, p value < 0.01). This association was not statistically significant in multivariable analyses (DFS: HR 1.09, 95CI 0.99–1.20, p value 0.08; DRFS: HR 1.03, 95CI 0.89–1.20, p value 0.67; OS: HR 1.11, 95CI 0.99–1.24, p value 0.08), whereas grade, tumour size, and nodal involvement were still prognostic for all end-points.

Conclusion: Worse prognostic factors such as higher grade, larger tumour size, and nodal involvement are associated with higher BMI in ER+/HER2− ILC, while there was no statistical evidence for an independent prognostic role for BMI. Therefore, we hypothesise that the effect of BMI on survival could be mediated through its association with these clinicopathological variables.

1. Introduction

Invasive lobular carcinoma (ILC) is the second most common type of breast cancer after invasive breast cancer of no special type (NST), representing up to 15% of all breast cancer diagnoses [1–3]. The hallmark of ILC is the loss of the cell–cell adhesion molecule E-cadherin, which leads to the infiltrative and discohesive growth of cancer cells [4]. The atypical growth pattern of ILC, without disruption of the normal structural and architectural features of breast tissue, makes it harder to detect these tumours by clinical examination and on standard mammography [5,6]. This may then lead to a delay in diagnosis, which could explain why tumours from patients with ILC are generally larger and present with more nodal involvement at the time of diagnosis as compared to patients with NST [3,7,8].

When looking at primary tumours, more than 90% of ILC express the oestrogen receptor (ER) [4,9,10]. Expression of the progesterone receptor (PR) is also more common in ILC than NST with more than 75% of ILC expressing PR [9,10]. Amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) is only present in 3–13% of ILC cases [11,12]. More than 80% of ILC is of low-to-intermediate histological grade [2,13,14]. Considering the treatment, there is a significant benefit of using aromatase inhibition over tamoxifen and no clear additional benefit of adding chemotherapy to endocrine regimens for patients with ER+ ILC [3,15,16]. Although a higher risk of developing metastatic disease for ILC as compared to NST has been described [7,17], other series have found a similar or even improved survival of patients with ILC [18,19].

The proportion of overweight and obese women has been increasing over the years, and body mass index (BMI) has been shown to be a complex yet important risk factor for the development of breast cancer in general [20,21]. It has been reported that a high BMI seems to protect against the development of premenopausal ER + breast cancer while increasing the risk of developing postmenopausal ER+ breast cancer [22–27]. BMI seems to similarly impact the risk of developing ILC and NST, although this is based on a limited amount of evidence [28,29].

For breast cancer in general, overweight and obesity have been associated with age, postmenopausal state, and unfavourable tumour characteristics such as larger tumours and higher rate of nodal involvement at diagnosis [30–32]. An association between a higher BMI and

an increased likelihood of a higher tumour grade has also been described [33].

A recent meta-analysis of 27 studies analysing the effect of obesity on breast cancer outcome in relation to cancer subtypes concluded that both disease-free survival (DFS) and overall survival (OS) were significantly worse in patients with obesity as compared to non-obese women without obesity [34]. This study, therefore, confirmed the earlier results of Chan et al. who performed a meta-analysis of 82 studies and described a poorer overall and breast cancer-specific survival both in pre- and postmenopausal obese women [35]. ILC was not analysed as a separate entity, and it is currently unknown if overweight and obesity affect the prognosis of patients with ILC. Here, we aimed to investigate in a large multicentric retrospective cohort of patients with ILC whether BMI is associated with disease-specific clinicopathological features and prognosis. Since the vast majority of ILC is ER+/HER2−, we focused our analyses on this subgroup and only conducted descriptive analyses in the other subgroups.

2. Patients and methods

2.1. Patients

Following approval by the ethics committee of the University Hospitals Leuven (S64063), we retrospectively assembled a multicentric cohort of 2856 female patients with known BMI (at diagnosis) diagnosed between January 2000 and December 2020 with non-metastatic pure (i.e. not mixed with other histological types) ILC in one of these five European centres (University Hospitals Leuven, Leuven, Belgium; GZA Hospital Sint-Augustinus, Antwerp, Belgium; Institut Jules Bordet, Brussels, Belgium; Institut Curie, Paris, France; Charité Universitätsmedizin, Berlin, Germany). These centres were chosen since there is an expertise in breast cancer research and a strong focus on ILC. The University Hospitals Leuven provided data of 1193 patients with ILC, GZA Hospitals Sint-Augustinus of 95 patients, Institut Bordet of 375 patients, Institut Curie of 713 patients, and Charité Universitätsmedizin of 480 patients. The following patient' and tumour' characteristics were collected: year of birth, age at diagnosis, BMI at primary diagnosis, menopausal state, diameter, TNM classification, pathology-based multifocality, grade, ER status, PR status, and HER2 status. For each patient, the use of radiotherapy and/or systemic (neo)adjuvant therapies was registered. Furthermore, the following event-related data were collected: locoregional recurrence, contralateral incidence, and distant recurrence with the respective dates of recurrence, as well as death, date of death, and cause of death.

BMI was categorised using the WHO classification into underweight (≤18.5 kg/m^2), lean (> 18.5 kg/m^2 and < 25 kg/m^2), overweight (≥25 kg/m^2 and < 30 kg/m^2), and obese (≥30 kg/m^2). Patients with underweight were seen as a separate category from lean patients since underweight might have a negative impact on breast cancer prognosis [36]. The following subgroups of ILC were defined: ER+/HER2−, ER−/HER2−, and HER2+. Historically, available immunohistochemistry (IHC) scores were used to define ER status. The Allred score [37] was used to determine ER positivity in GZA Hospitals Sint-Augustinus, Institut Jules Bordet, and for patients diagnosed from 2004 onward in University Hospitals Leuven. A score of 0–2 was seen as negative, a score of 5–8 was seen as positive, and a score of 3–4 was seen as unknown unless more information about the composition of the score was available, making tumours with ≥1% of positive cells with at least weak staining being interpreted as being ER+. For patients diagnosed between 2000 and 2003 at University Hospitals Leuven, the H-score [38] and/or Allred score were used. In case no Allred score was available, an H-score of 1 was considered to be positive. Charité Universitätsmedizin reported the ER score in percentage and also used a cutoff of 1% of positive cells to define an ER+ tumour. Institut Curie followed the French guidelines [39], which state that 10% of the cells need to be positive in order to consider a tumour ER+. In all centres, HER2 was first assessed using IHC and scored according to the respective guidelines of the American Society of Clinical Oncology at the time of diagnosis [40]. A score of 0–1+ was seen as negative, and a score of 3+ was seen as positive. Tumours with a score of 2+ were further evaluated using fluorescence in situ hybridisation (FISH) in Germany and France. In Belgium, all cases with scores 2+ and 3+ were tested by FISH to exclude or confirm *HER2* amplification based on guidelines at the time of diagnosis.

2.2. Statistical analyses

The following standard clinicopathological variables besides BMI were defined to be included in the association and survival analyses: age, grade, tumour size, nodal involvement, multifocality, and PR expression. The association of BMI as a continuous dependent variable with clinicopathological variables was assessed using linear regression models: Model 1 was adjusted for the centre (further referred to as a univariable model), and Model 2 was additionally adjusted for all considered variables (further referred to as a multivariable model). Similarly, the association of BMI as a categorical variable with clinicopathological variables was evaluated using multinomial logistic regression models with 'lean' as the baseline category. Quantile regression models equivalent to Models 1 and 2 were performed for the 0.1-, 0.25-, 0.5-, 0.75-, and 0.9-quantiles of the conditional distribution of BMI to explore varying associations of BMI with standard clinicopathological features along its spectrum.

DFS was defined as the time from diagnosis to the first event of either locoregional recurrence, contralateral

recurrence, distant recurrence, or death; distant recurrence-free survival (DRFS) as the time from diagnosis to the first event of distant recurrence; and OS as the time from diagnosis to death from any cause. The median follow-up was calculated using the reverse Kaplan–Meier estimator. The Kaplan–Meier method was first used to estimate the rates of DFS and OS in patients of different BMI categories. Crude cumulative incidence curves accounting for death without distant recurrence as the sole competing event were constructed for inspection of event rates of DRFS according to BMI categories. Non-breast primary tumours and their related survival events could not be considered in our analyses as these data were not available. Models 1 (stratified by centre) and 2 (adjusted for standard clinicopathological variables and treatment and stratified by centre) Cox regression models were next performed to quantify the association of BMI either as a continuous or categorical variable with DFS and OS. Potential non-linear effects of continuous BMI on DFS and OS were explored using a restricted cubic spline in the Cox models. Models with linear and non-linear effects were comparatively evaluated by the computation of AIC and a likelihood-ratio (LR) test. Cox regression models including non-linear effects did not statistically differ from linear models for the effect of BMI on survival, indicating that the linear models were possibly suited for describing the data. DRFS was analysed in the presence of death without distant recurrence as the competing risk using Fine-Grey subdistribution hazard regression models: Model 1 was adjusted for the centre, and Model 2 was additionally adjusted for all considered variables. For simplicity, Models 1 and 2 will be subsequently referred to as univariable and multivariable models, respectively, in the text. Statistical analyses were performed using R version 4.1.1. All statistical tests were considered statistically significant when the p value < 0.05 was a standard evidence criterion.

3. Results

3.1. Patient population

In this study, we considered 2856 patients diagnosed with ILC for which the BMI at diagnosis was available. Of these 2856 patients, 88 were underweight (3.1%), 1572 were lean (55.0%), 784 were overweight (27.5%), and 412 were obese (14.4%). The majority (n = 2570, 90.0%) was diagnosed with ER+/HER2− ILC. Only 49 patients (1.7%) were diagnosed with ER−/HER2− ILC and 95 patients (3.3%) with HER2+ ILC. Within the ER+/HER2− subtype, 80 patients were underweight (3.1%), 1410 were lean (54.9%), 712 were overweight (27.7%), and 368 were obese (14.3%). Since only a minority of patients were underweight, these patients were excluded from further analyses. Patient and tumour characteristics of patients with ER+/HER2− ILC who are lean, overweight, or obese are summarised in Table 1.

Forty-two patients with ER−/HER2− ILC had information available on BMI, of which 27 (64.3%) were lean, 10 (23.8%) were overweight, and 5 (11.9%) were obese. Ninety-one patients with HER2+ ILC had information on BMI available, of which 57 (62.6%) were lean, 22 (24.2%) were overweight, and 12 (13.2%) were obese. Clinicopathological features of these populations are available in Supplementary Tables 1 and 2.

Since the results of the global cohort would be driven by the patients with ER+/HER2− ILC, our analyses focused on the ER+/HER2− subgroup, whereas the other subgroups were approached in a descriptive manner.

3.2. Association of BMI at primary diagnosis with standard clinicopathological features

We investigated the association between BMI, as a continuous variable, and clinicopathological features of ILC for the ER+/HER2− cohort using regression analyses (Fig. 1). For these patients, a larger tumour size (≥2 cm compared to < 2 cm), nodal involvement at the time of diagnosis, higher grade (grade 3 versus grade 1 or 2), pathological multifocality, as well as PR expression were associated with a higher BMI. Similar results were seen when looking at BMI as a categorical variable, with the exception of PR expression not presenting statistical evidence but retaining the direction of the association. Quantile regressions suggested a non-linear association between BMI and clinicopathological features, albeit all in a consistent direction (Supplementary Fig. 1).

With regard to the ER−/HER2− ILC subgroup (Supplementary Table 1), while 92.6% of the lean patients and 90.0% of the patients with overweight were older than 50 at diagnosis, only 60.0% of the patients with obesity fell into this age category. Similarly, regarding the ER+/HER2− cohort, patients with obesity had more often larger tumours (≥2 cm: 100% versus 44.4%), nodal involvement (60.0% versus 33.3%), and a higher tumour grade (grade 3: 60.0% versus 25.9%) than lean patients.

In patients with HER2+ ILC (Supplementary Table 2), 91.7% of the patients with obesity were > 50-years old at the time of diagnosis. For lean patients, this was 82.5%, and for patients with overweight, it was 81.8%. Lean patients had a grade 3 tumour in 41.8% of the cases, whereas, for patients with overweight and obesity, it was found in 33.3% of the cases. In, respectively, 52.6%, 72.7%, and 41.7% of the lean patients and patients with overweight and obesity, the tumour was found to be ≥2 cm. Patients with overweight and obesity had nodal involvement in 68.2% and 58.3% of the cases, respectively, whereas lean patients only had nodal involvement in 40.4% of the cases. ER expression was found in 77.2% of the lean cases, 81.0% of the patients with overweight, and 83.3% of the patients with obesity. PR expression was found to be present in the tumours of 57.4% of the

Table 1
Patient and tumour characteristics for lean patients and patients with overweight or obesity with ER+/HER2− ILC.

Characteristic	*All*		*Lean*		*Overweight*		*Obese*	
	N (Total = 2490)	**%**	**N (Total = 1410)**	**%**	**N (Total = 712)**	**%**	**N (Total = 368)**	**%**
Age								
≤50	589	23.7	413	29.3	128	18.0	48	13.0
>50	1901	76.3	997	70.7	584	82.0	320	87.0
Missing	0		0		0		0	
Menopausal state								
Premenopausal	579	25.5	396	31.3	131	19.8	52	15.2
Postmenopausal	1690	74.5	868	68.7	531	80.2	291	84.8
Missing	221		146		50		25	
Tumour size								
<2 cm	1109	45.0	715	51.1	286	40.7	108	29.8
≥2 cm	1355	55.0	684	48.9	417	59.3	254	70.2
Missing	26		11		9		6	
Nodal involvement								
No	1473	63.2	908	67.6	398	60.6	167	50.3
Yes	859	36.8	435	32.4	259	39.4	165	49.7
Missing	158		67		55		36	
Histological grade								
1 and 2	2158	91.9	1265	93.8	597	90.6	296	86.8
3	190	8.1	83	6.2	62	9.4	45	13.2
Missing	142		62		53		27	
PR expression								
PR+	1987	86.3	1092	85.2	582	87.5	304	87.9
PR−	315	13.7	190	14.8	83	12.5	42	12.1
Missing	197		128		47		22	
Focality								
Unifocal	1357	72.2	799	73.6	391	71.4	167	67.6
Multifocal	523	27.8	286	26.4	157	28.6	80	32.4
Missing	610		325		164		121	
Radiotherapy								
Yes	2067	84.0	1155	82.9	606	85.8	306	84.5
No	395	16.0	239	17.1	100	14.2	56	15.5
Missing	28		16		6		6	
Chemotherapy								
Yes	613	24.8	323	23.1	185	26.2	105	28.9
No	1856	75.2	1078	76.9	520	73.8	258	71.1
Missing	21		9		7		5	
Endocrine treatment								
Yes	2328	95.6	1308	94.7	668	96.3	352	97.8
No	107	4.4	73	5.3	26	3.7	8	2.2
Missing	55		29		18		8	

N, number; PR, progesterone receptor

lean patients 77.3% and 83.3% of the patients with overweight and obesity, respectively.

3.3. Association between BMI at primary diagnosis and survival

The median follow-up time was 99.96 months (IQR 59.28–137.52) for the ER+/HER2− subgroup of 2570 patients. The Kaplan–Meier curves for DFS and OS for this subgroup as well as the cumulative index curve for DRFS suggest a worse prognosis in patients with overweight and obesity (Fig. 2). However, in multivariable analyses, the association of BMI with a worse DFS, DRFS, or OS was no longer statistically significant (Fig. 3, Supplementary Fig. 2 for the entire ILC cohort). Higher tumour grade, larger tumour size, and the presence of affected lymph nodes did remain associated with worse survival in multivariable analyses for all end-points. Additionally, higher age at diagnosis was associated with worse DFS and OS, and the administration of radiotherapy and chemotherapy was associated with better DFS and OS in the multivariable analyses (Figs. 3A and C). When looking at BMI as a continuous variable, similar results were observed (Fig. 3). BMI did not remain significantly associated with DFS, DRFS, or OS in multivariable analyses, although a consistent trend was seen for the three end-points (with all p values < 0.10).

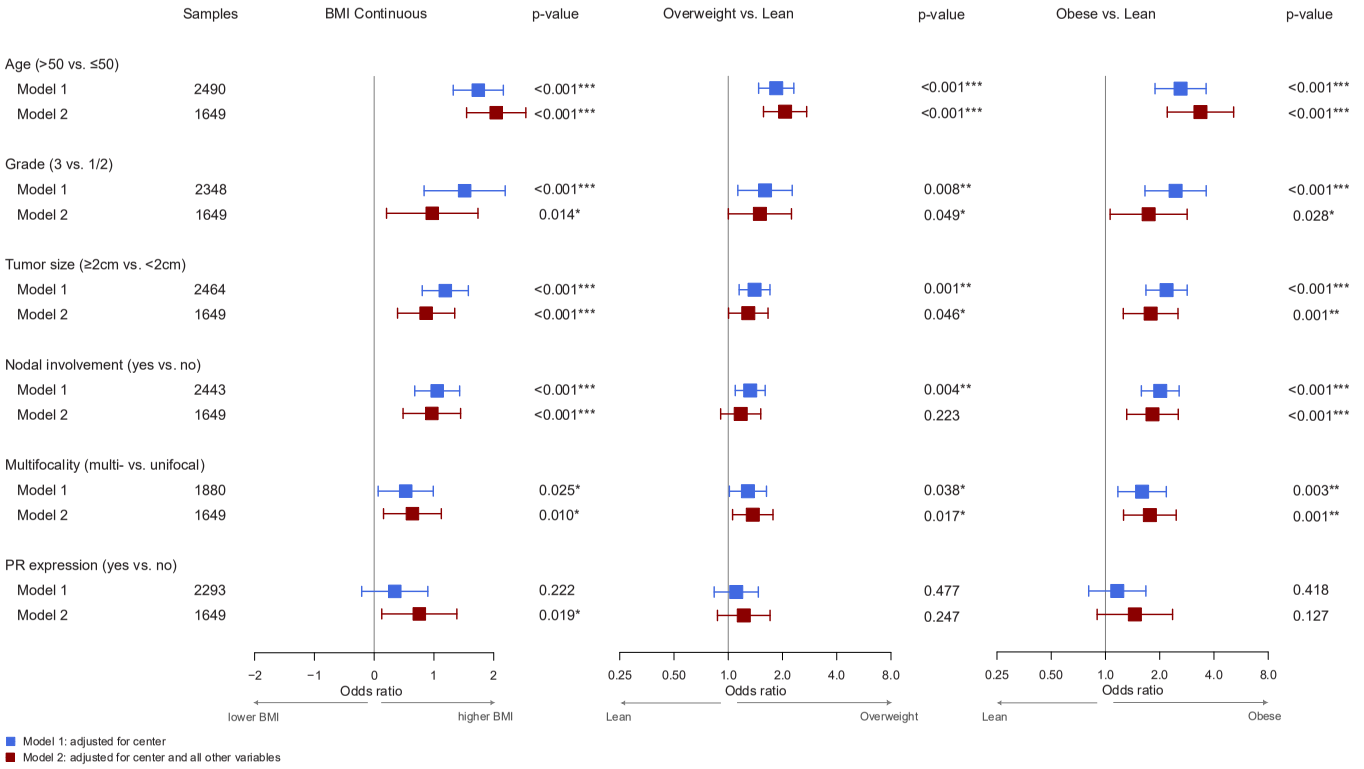

Fig. 1. Forest plot of association of clinicopathological features of ER+/HER2− ILC with continuous and categorical BMI at diagnosis. Legend: On the left side, the association of clinicopathological features of ER+/HER2− ILC is shown with BMI as a continuous variable; in the middle, the association of clinicopathological features of ER+/HER2− ILC is shown with lean versus overweight; on the right side, the association of clinicopathological features of ER+/HER2− ILC is shown with lean versus obesity. BMI is the outcome variable in all the models. FDR, false discovery rate; OR, odds ratio; PR, progesterone receptor; BMI, body mass index; ER, oestrogen receptor; HER2, human epidermal growth factor receptor; ILC, invasive lobular breast cancer; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

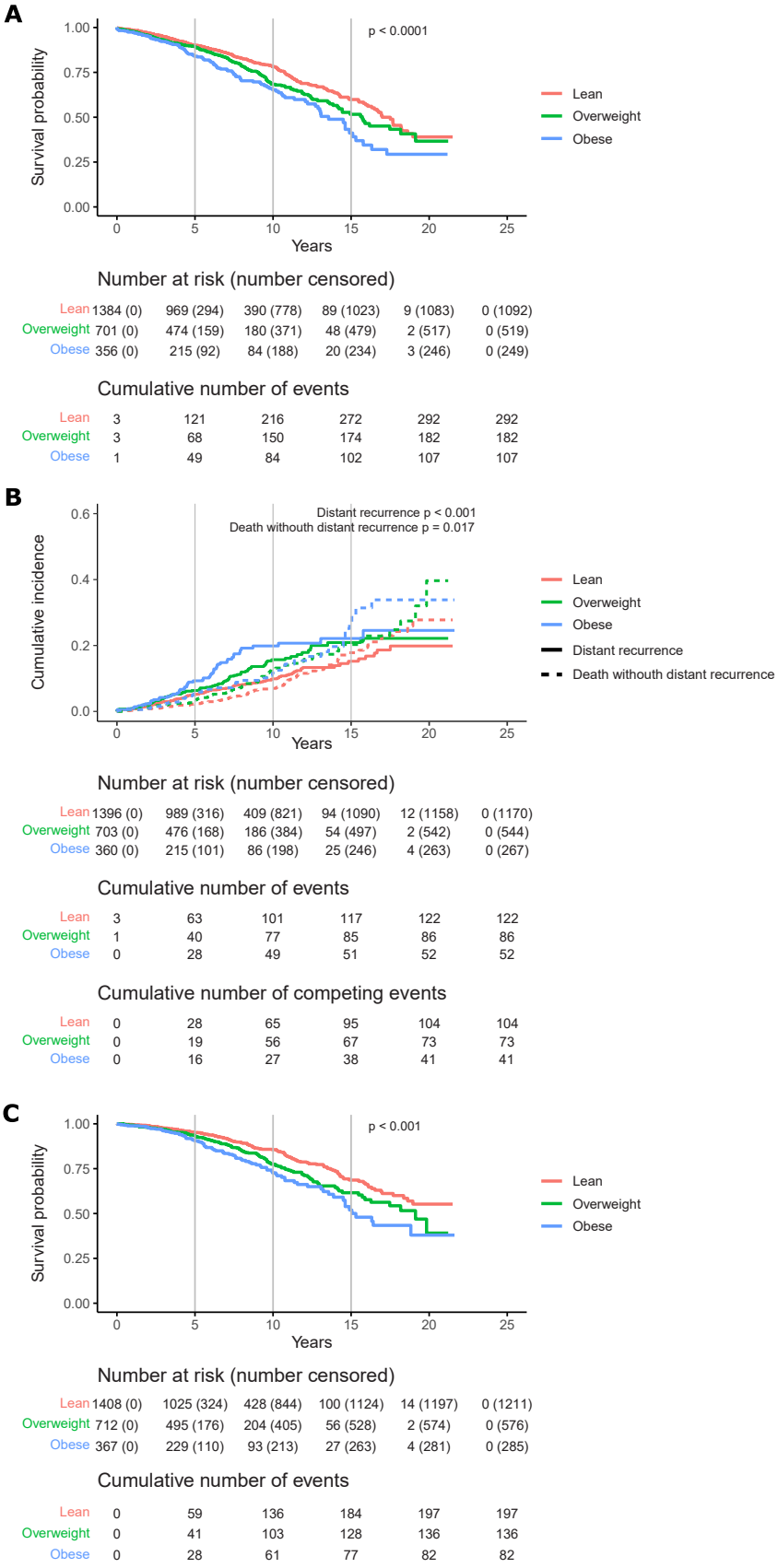

Fig. 2. DFS, DRFS, and OS by BMI at diagnosis in patients with ER+/HER2− ILC. Panels A and C show the Kaplan–Meier curves of, respectively, disease-free survival and overall survival probabilities in patients of different BMI categories; panel B shows the cumulative incidence curves of distant recurrence-free survival events in patients of different BMI categories.

In the Kaplan–Meier curves for the 49 patients with an ER−/HER2− ILC (Supplementary Fig. 3), no clear difference was seen for DFS between lean and obesity patients. Considering DRFS and OS, it seemed that patients with obesity have a trend towards worse prognosis than lean patients. For the 95 patients with HER2+ ILC, DFS, DRFS, and OS seemed to be better in the patients with obesity as compared to the lean patients, but this should be interpreted with caution due to the small sample size (Supplementary Fig. 4). As sample sizes were limited for both ER−/HER2− and HER2+ ILC subgroups, regression analyses were not performed.

4. Discussion

In this study, we showed that the clinicopathological features of ER+/HER2− ILC at diagnosis, like higher grade, larger tumour size, nodal involvement, and multifocality, are associated with a higher BMI at diagnosis. Since the ageing process in postmenopausal women is associated with an increase in BMI in the general population [41], it was to be expected that, in patients > 50 years, a higher BMI was seen. As in other, but not lobular-specific, retrospective studies of breast cancer [30,31], the presence of larger tumours and higher likelihood of nodal involvement in association with higher BMI categories was confirmed. It is hypothesised that, in women with a higher BMI, the diagnosis of breast cancer might be delayed since masses are more difficult to palpate in larger breasts [42]. However, ILC does not often present as a palpable mass [43]; thus, other underlying factors seem to play a role when it comes to ILC. Furthermore, Hellmann et al. reported a lower participation in organised screening in women who were underweight and in women who were morbidly obese [44]. Since BMI and age are inversely associated with breast density, the detection of suspicious masses on screening mammography should be easier in overweight and obese postmenopausal women [45,46].

Underlying biological mechanisms in women with excess body weight might have an impact on tumour progression. It has been suggested that, especially for ER-dependent tumours, an excess of adipose tissue with increased aromatisation activity can lead to higher levels of oestrogen, which can promote tumour growth [47]. Additionally, obesity leads to a higher likelihood of insulin resistance and increased activation of insulin-like growth factor pathways, more inflammatory cytokines, more adipokines, and more oxidative stress, enhancing further tumour development [48]. Although the vast majority of ILC have a low to intermediate histological grade, ER+/HER2− ILC was associated with higher histological grade in patients with overweight and obesity at diagnosis in our study. Other studies have shown similar associations between excess body weight and a higher histological grade in breast cancer [33,49]. The aforementioned underlying biological mechanisms associated with obesity might play a role in the aggressiveness of tumours and may lead to a higher grade at diagnosis [50].

Focality in association with BMI has only rarely been investigated in patients with breast cancer. In this study, a higher likelihood of multifocality was associated with overweight and obesity in patients with ILC. This is in contrast with the findings of Haakinson et al. showing that a high BMI (> 30 kg/m^2 was associated with a lower incidence of multifocality in breast cancer cases [51]. However, ILC represented only a minority (13% of 1352 patients) of the included cases. Other investigators found no significant association between a BMI ≥25 kg/m^2 and multifocality in comparison to a BMI between 18.5 and 24.9 kg/m^2 in patients with breast cancer [52].

Both fundamental research and clinical research have shown that obesity increases the likelihood of an ER+/HER2− breast tumour to also express PR [27,53–55]. It is thought that obesity in postmenopausal women induces increased levels of circulating oestrogen by a decrease in sex hormone binding globulin, which in turn leads to an increase in PR expression [27,56]. Although, in our series, PR expression was significantly associated with BMI as a continuous variable, only a trend towards more PR-positive ER+/HER2− ILC tumours diagnosed in patients with overweight and obesity was seen when considering BMI as a categorical variable. PR expression is a known prognostic factor of breast cancer, especially in ER+/HER2− breast cancer where PR positivity seems to be associated with better outcome [57]. While some studies had suggested a better response to endocrine treatment of PR+ tumours [58], this could not be confirmed in a meta-analysis [59].

BMI seemed to be prognostic for DFS, DRFS, and OS in patients with ER+/HER2− ILC when evaluated by univariable regression models and the survival curves. Yet, in multivariable analyses, the effect did not remain statistically significant. However, there was still a noticeable trend towards worse outcomes, especially when BMI was considered as a continuous variable. Since BMI is associated with worse clinicopathological features, we hypothesise that the prognostic effect of BMI might be mediated through these variables for patients with ER+/HER2− ILC. Blair et al. came to a similar conclusion that the effect of BMI on prognosis might be underestimated in multivariable models due to the interaction with included clinicopathological features [33].

Considering the patients with ER−/HER2− ILC, a lower age at diagnosis and tumours with a higher grade, a larger size, and a higher likelihood of nodal involvement seemed to be more present in patients with obesity as compared to lean patients. In patients with HER2+ ILC, patients with obesity were older at diagnosis and were diagnosed more often with lower grade tumours, which were more likely to express ER

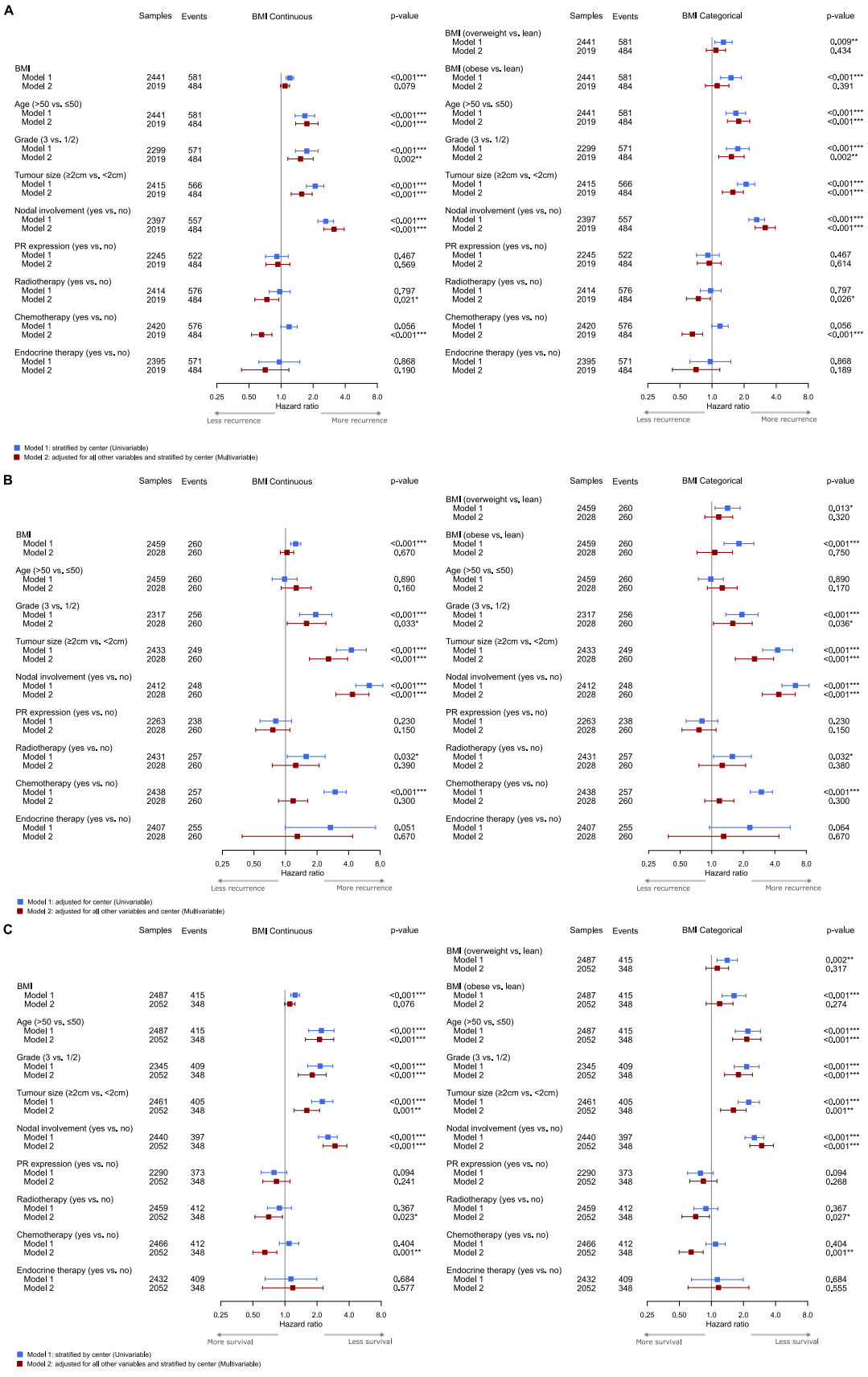
A
Samples
Events
BMI Continuous
p-value
BMI
Model 1 2441 581 <0.001***
Model 2 2019 484 0.079
Age (>50 vs. ≤50)
Model 1 2441 581 <0.001***
Model 2 2019 484 <0.001***
Grade (3 vs. 1/2)
Model 1 2299 571 <0.001***
Model 2 2019 484 0.002**
Tumour size (≥2cm vs. <2cm)
Model 1 2415 566 <0.001***
Model 2 2019 484 <0.001***
Nodal involvement (yes vs. no)
Model 1 2397 557 <0.001***
Model 2 2019 484 <0.001***
PR expression (yes vs. no)
Model 1 2245 522 0.467
Model 2 2019 484 0.569
Radiotherapy (yes vs. no)
Model 1 2414 576 0.797
Model 2 2019 484 0.021*
Chemotherapy (yes vs. no)
Model 1 2420 576 0.056
Model 2 2019 484 <0.001***
Endocrine therapy (yes vs. no)
Model 1 2395 571 0.868
Model 2 2019 484 0.190
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
Less recurrence
More recurrence
BMI Categorical
p-value
BMI (overweight vs. lean)
Model 1 2441 581 0.009**
Model 2 2019 484 0.434
BMI (obese vs. lean)
Model 1 2441 581 <0.001***
Model 2 2019 484 0.391
Age (>50 vs. ≤50)
Model 1 2441 581 <0.001***
Model 2 2019 484 <0.001***
Grade (3 vs. 1/2)
Model 1 2299 571 <0.001***
Model 2 2019 484 0.002**
Tumour size (≥2cm vs. <2cm)
Model 1 2415 566 <0.001***
Model 2 2019 484 <0.001***
Nodal involvement (yes vs. no)
Model 1 2397 557 <0.001***
Model 2 2019 484 <0.001***
PR expression (yes vs. no)
Model 1 2245 522 0.467
Model 2 2019 484 0.614
Radiotherapy (yes vs. no)
Model 1 2414 576 0.797
Model 2 2019 484 0.026*
Chemotherapy (yes vs. no)
Model 1 2420 576 0.056
Model 2 2019 484 <0.001***
Endocrine therapy (yes vs. no)
Model 1 2395 571 0.868
Model 2 2019 484 0.189
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
Less recurrence
More recurrence
Model 1: stratified by center (Univariable)
Model 2: adjusted for all other variables and stratified by center (Multivariable)
B
Samples
Events
BMI Continuous
p-value
BMI
Model 1 2459 260 <0.001***
Model 2 2028 260 0.670
Age (>50 vs. ≤50)
Model 1 2459 260 0.890
Model 2 2028 260 0.160
Grade (3 vs. 1/2)
Model 1 2317 256 <0.001***
Model 2 2028 260 0.033*
Tumour size (≥2cm vs. <2cm)
Model 1 2433 249 <0.001***
Model 2 2028 260 <0.001***
Nodal involvement (yes vs. no)
Model 1 2412 248 <0.001***
Model 2 2028 260 <0.001***
PR expression (yes vs. no)
Model 1 2263 238 0.230
Model 2 2028 260 0.150
Radiotherapy (yes vs. no)
Model 1 2431 257 0.032*
Model 2 2028 260 0.390
Chemotherapy (yes vs. no)
Model 1 2438 257 <0.001***
Model 2 2028 260 0.300
Endocrine therapy (yes vs. no)
Model 1 2407 255 0.051
Model 2 2028 260 0.670
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
Less recurrence
More recurrence
BMI Categorical
p-value
BMI (overweight vs. lean)
Model 1 2459 260 0.013*
Model 2 2028 260 0.320
BMI (obese vs. lean)
Model 1 2459 260 <0.001***
Model 2 2028 260 0.750
Age (>50 vs. ≤50)
Model 1 2459 260 0.890
Model 2 2028 260 0.170
Grade (3 vs. 1/2)
Model 1 2317 256 <0.001***
Model 2 2028 260 0.036*
Tumour size (≥2cm vs. <2cm)
Model 1 2433 249 <0.001***
Model 2 2028 260 <0.001***
Nodal involvement (yes vs. no)
Model 1 2412 248 <0.001***
Model 2 2028 260 <0.001***
PR expression (yes vs. no)
Model 1 2263 238 0.230
Model 2 2028 260 0.150
Radiotherapy (yes vs. no)
Model 1 2431 257 0.032*
Model 2 2028 260 0.380
Chemotherapy (yes vs. no)
Model 1 2438 257 <0.001***
Model 2 2028 260 0.300
Endocrine therapy (yes vs. no)
Model 1 2407 255 0.064
Model 2 2028 260 0.670
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
Less recurrence
More recurrence
Model 1: adjusted for center (Univariable)
Model 2: adjusted for all other variables and center (Multivariable)
C
Samples
Events
BMI Continuous
p-value
BMI
Model 1 2487 415 <0.001***
Model 2 2052 348 0.076
Age (>50 vs. ≤50)
Model 1 2487 415 <0.001***
Model 2 2052 348 <0.001***
Grade (3 vs. 1/2)
Model 1 2345 409 <0.001***
Model 2 2052 348 <0.001***
Tumour size (≥2cm vs. <2cm)
Model 1 2461 405 <0.001***
Model 2 2052 348 0.001**
Nodal involvement (yes vs. no)
Model 1 2440 397 <0.001***
Model 2 2052 348 <0.001***
PR expression (yes vs. no)
Model 1 2290 373 0.094
Model 2 2052 348 0.241
Radiotherapy (yes vs. no)
Model 1 2459 412 0.367
Model 2 2052 348 0.023*
Chemotherapy (yes vs. no)
Model 1 2466 412 0.404
Model 2 2052 348 0.001**
Endocrine therapy (yes vs. no)
Model 1 2432 409 0.684
Model 2 2052 348 0.577
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
More survival
Less survival
BMI Categorical
p-value
BMI (overweight vs. lean)
Model 1 2487 415 0.002**
Model 2 2052 348 0.317
BMI (obese vs. lean)
Model 1 2487 415 <0.001***
Model 2 2052 348 0.274
Age (>50 vs. ≤50)
Model 1 2487 415 <0.001***
Model 2 2052 348 <0.001***
Grade (3 vs. 1/2)
Model 1 2345 409 <0.001***
Model 2 2052 348 <0.001***
Tumour size (≥2cm vs. <2cm)
Model 1 2461 405 <0.001***
Model 2 2052 348 0.001**
Nodal involvement (yes vs. no)
Model 1 2440 397 <0.001***
Model 2 2052 348 <0.001***
PR expression (yes vs. no)
Model 1 2290 373 0.094
Model 2 2052 348 0.268
Radiotherapy (yes vs. no)
Model 1 2459 412 0.367
Model 2 2052 348 0.027*
Chemotherapy (yes vs. no)
Model 1 2466 412 0.404
Model 2 2052 348 0.001**
Endocrine therapy (yes vs. no)
Model 1 2432 409 0.684
Model 2 2052 348 0.555
0.25 0.50 1.0 2.0 4.0 8.0
Hazard ratio
More survival
Less survival
Model 1: stratified by center (Univariable)
Model 2: adjusted for all other variables and stratified by center (Multivariable)

Fig. 3. Forest plot of the association of clinicopathological features of ER+/HER2− ILC with DFS, DRFS, and OS. Panels A and C show the forest plots presenting the association of BMI with disease-free survival and overall survival, respectively, quantified by Cox models: Model 1 was stratified by centre, and Model 2 was adjusted for all included variables and stratified by centre. Panel B shows the forest plots presenting the association of BMI with distant recurrence-free survival quantified by Fine-Grey regression models: Model 1 was adjusted for centre, and Model 2 was adjusted for the centre and all included variables. On the left side of panels A, B, and C, the results are shown with BMI considered as a continuous variable with an increment of 5 kg/m^2; on the right side of panels A, B, and C, the results are shown with BMI considered as a categorical variable. DFS, disease-free survival; DRFS, distant recurrence-free survival; OS, overall survival; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

and PR as compared to lean patients. Kaplan–Meier curves at first sight showed a worse prognosis in patients with obesity with ER−/HER2− ILC and an improved prognosis in HER2+ ILC. However, the number of patients included with an ER−/HER2− ILC or HER2+ ILC was small and only allowed descriptive analyses. Therefore, it is not possible to make definitive conclusions on these subtypes. Further analyses of less common subtypes of ILC are needed. Furthermore, it is unsure if our findings apply to all different histotypes of ILC [12].

Our study presents several limitations, which are inherent to retrospective studies. First, no central pathology confirmation for ILC was performed, and pathological diagnosis of ILC has evolved over the years and can vary from one pathology laboratory to another, with approximately half of the pathology labs using E-cadherin IHC to confirm ILC diagnosis [60,61]. In this study, we only considered centres who have a special interest in ILC and have pathology departments specialised in the differentiation between ILC and NST tumours. Second, differences between centres exist in the scoring systems used for the interpretation of ER and PR. Third, due to a rather larger window of inclusion (2000–2020), differences in diagnostic and treatment approaches need to be considered, and the latter might impact survival data. Furthermore, since the cause of death was missing for more than half of the deceased patients, we could not perform cancer-specific OS analyses. Finally, here we only considered BMI at diagnosis, while it is known to be a dynamic variable in a patient's life. Changes in BMI before diagnosis may have had an impact on ILC development and the diagnosis of ILC [62], whereas changes in body weight occurring after the diagnosis may impact the efficacy of treatments and may influence survival data [22–26,63].

Furthermore, BMI is often used as a surrogate marker of adiposity, but it does not always correlate well with the metabolic effect of adipose tissue in patients [64]. Other clinical and histological surrogates of adiposity might reflect better its impact on disease onset and progression [65–67]. Prospective trials that approach adiposity clinically by the use of BMI, waist circumference, waist-hip ratio, bio-impendence measurements, adiposity measurements by imaging, or histologically by measuring the size of adipose cells and looking at inflammatory parameters may help understand the direct effect of adipose tissue on breast cancer cells. The FATLAS trial (NCT04200768), which is currently ongoing in the University Hospitals of Leuven, Belgium, aims at a multilevel characterisation of systemic and mammary adiposity in breast cancer patients. Moreover, FATLAS has a prespecified substudy on ILC. Despite both of the abovementioned limitations about BMI, the current study still contributes greatly to the understanding of the impact of adiposity on ILC, since this is one of the largest multicentric retrospective trials on patients diagnosed with ILC with data on BMI.

To conclude, the association between worse clinicopathological features like higher tumour grade, larger tumour size, and higher likelihood of nodal involvement with a higher BMI at diagnosis that is known for patients with breast cancer was also seen in patients with ER+/HER2− ILC. In multivariable survival analyses, although BMI displayed a modest positive association with poorer outcomes, it did not present strong statistical evidence of being an independent prognostic factor. The clinicopathological features that are known for their prognostic importance in luminal tumours (e.g. tumour grade, tumour size, and nodal status) remained strongly prognostic in our analyses. We hypothesise that the effect of BMI on survival could be largely mediated through these variables for patients with ER+/HER2− ILC. Further fundamental and clinical research analysing the effects of BMI or alternative measures of adiposity on the development, biology, and progression of ILC, as well as on the efficacy of treatment regimens in patients with ILC, are needed.

Disclaimers

The authors have declared no conflicts of interest related to this current work.

Funding

The study was funded by the Luxembourg Cancer Foundation (grant FC/2018/07) and the Consolidator Grant approved by the European Research Council (ERC, FAT-BC 101003153). MDS is funded by the KU Leuven Fund Nadine de Beauffort. TG and FR are

funded by FWO through a research fellowship. GF is the recipient of a postdoctoral mandate from the KOOR of the UH-Leuven. Finally, KVB is funded by the KU Leuven Fund Nadine de Beauffort and a Conquer Cancer – Lobular Breast Cancer Alliance Young Investigator Award for Invasive Lobular Carcinoma Research, supported by the Lobular Breast Cancer Alliance. Any opinions, findings, and conclusions expressed in this material are those of the author (s) and do not necessarily reflect those of the American Society of Clinical Oncology®, Conquer Cancer®, or Lobular Breast Cancer Alliance.

CRediT authorship contribution statement

Karen Van Baelen: Conceptualization; Methodology; Data curation; Writing – original draft; Visualization. **Ha-Linh Nguyen**: Conceptualization; Methodology; Formal analysis; Data curation; Writing – original draft. **François Richard:** Conceptualization; Methodology; Formal analysis; Writing – review & editing. **Anne-Sophie Hamy-Petit, Maria Margarete Karsten, Guilherme Nader Marta, Peter Vermeulen, Aullene Toussaint, Fabien Reyal, Anne Vincent-Salomon, Luc Dirix, Hilde Wuyts, Adam David Dordevic, Evandro de Azambuja, Denis Larsimont, Ottavia Amato, Maxim De Schepper, Tatjana Geukens, Sileny N. Han, Thaïs Baert, Kevin Punie, Hans Wildiers, Chantal Remmerie, Ann Smeets, Ines Nevelsteen, Giuseppe Floris, Patrick Neven:** Data curation; Writing – review & editing. **Marion Maetens:** Project administration; Funding acquisition; Writing – review & editing. **Elia Biganzoli:** Methodology; Formal analysis; Writing – review & editing. **Christine Desmedt:** Conceptualization; Methodology; Supervision; Funding acquisition; Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This article/publication is based upon work from the European Lobular Breast Cancer Consortium (ELBCC) and the COST Action LOBSTERPOT CA19138, supported by COST (European Cooperation in Science and Technology, www.cost.eu).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.112988.

References

[1] Sledge GW, Chagpar A, Perou C. Collective wisdom: lobular carcinoma of the breast. Am Soc Clin Oncol Educ Book 2016:18–21. https://doi.org/10.1200/edbk_100002.
[2] Reed MEMC, Kutasovic JR, Lakhani SR, Simpson PT. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. Breast. Cancer Res 2015;17:12.
[3] Van Baelen K, Geukens T, Maetens M, Tjan-Heijnen V, Lord CJ, Linn S, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol 2022;33:769–85. https://doi.org/10.1016/J.ANNONC.2022.05.006.
[4] Christgen M, Steinemann D, Kühnle E, Länger F, Gluz O, Harbeck N, et al. Lobular breast cancer: clinical, molecular and morphological characteristics. Pathol Res Pract 2016;212:583–97.
[5] Weaver O, Yang W. Imaging of breast cancers with predilection for nonmass pattern of growth: invasive lobular carcinoma and DCIS—does imaging capture it all? Am J Roentgenol 2020;215:1504–11.
[6] Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: imaging. Breast Cancer Res 2015;17:94.
[7] Pestalozzi BC, Zahrieh D, Mallon E, Gusterson BA, Price KN, Gelber RD, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol 2008;26:3006–14.
[8] Corona SP, Bortul M, Scomersi S, Bigal C, Bottin C, Zanconati F, et al. Management of the axilla in breast cancer: outcome analysis in a series of ductal versus lobular invasive cancers. Breast Cancer Res Treat 2020;180:735–45.
[9] Sharma SDJ, Barry M, O'Reilly EA, Kell MR. Surgical management of lobular carcinoma from a national screening program: A retrospective analysis. Eur J Surg Oncol 2015;41:79–85.
[10] Biglia N, Maggiorotto F, Liberale V, Bounous VE, Sgro LG, Pecchio S, et al. Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). Eur J Surg Oncol 2013;39:455–60.
[11] Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathol 2020;77:181–5.
[12] Christgen M, Cserni G, Floris G, Marchio C, Djerroudi L, Kreipe H, et al. Lobular breast cancer: histomorphology and different concepts of a special spectrum of tumors. Cancers 2021;13:3695.
[13] Ciriello G, Gatza ML, Beck AH, Wilkerson MD, Rhie SK, Pastore A, et al. Comprehensive molecular portraits of invasive lobular breast cancer. Cell 2015;163:506–19.
[14] Mersin H, Yildirim E, Gülben K, Berberoğlu A. In invasive lobular carcinoma different from invasive ductal carcinoma? Eur J Surg Oncol 2003;29:390–5.
[15] Metzger O, Giobbie-Hurder A, Mallon E, Gusterson B, Viale G, Winer EP, et al. Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial. J Clin Oncol 2015;33:2772–85.
[16] Yaghi M, Bilani N, Dominguez B, Zerdan MB, Li H, Saravia D, et al. Efficacy of chemotherapy in patients with HR +/HER2–invasive lobular breast cancer. Cancer Treat Res Commun 2023;34:100666.
[17] Adachi Y, Ishiguro J, Kotani H, Hisada T, Ichikawa M, Gondo N, et al. Comparison of clinical outcomes between luminal invasive ductal carcinoma and luminal invasive lobular carcinoma. BMC Cancer 2016;16:248.
[18] Timbres J, Moss C, Mera A, Haire A, Gillett C, Van Hemelrijck M, et al. Survival outcomes in invasive lobular carcinoma compared to oestrogen receptor-positive invasive ductal carcinoma. Cancers 2021;13:3036.

[19] Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau SW, Broglio K, Theriault RL, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 2005;23:41–8.
[20] Liu K, Zhang W, Dai Z, Wang M, Tian T, Liu X, et al. Association between body mass index and breast cancer risk: evidence based on a dose–response meta-analysis. Cancer Manag Res 2018;10:143.
[21] Di Cesare M, Bentham J, Stevens GA, Ruhli F, Staub K, Faeh D, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–96.
[22] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. Adults. N Engl J Med 2003;348:1625–38.
[23] Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011;29:25–31.
[24] Sparano JA, Zhao F, Martino S, Ligibel JA, Perez EA, Saphner T, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol 2015;33:2353–60.
[25] Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. J Clin Oncol 2016;34:4203–16.
[26] Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer–viewpoint of the IARC Working Group. N Engl J Med 2016;375:794–8.
[27] Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status-a meta-analysis. Int J Cancer 2009;124:698–712.
[28] Kotsopoulos J, Chen WY, Gates MA, Tworoger SS, Hankinson SE, Rosner BA. Risk factors for ductal and lobular breast cancer: results from the nurses' health study. Breast Cancer Res 2010;12:R106.
[29] Feigelson HS, Patel AV, Teras LR, Gansler T, Thun MJ, Calle EE. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. Cancer 2006;107:12–21.
[30] Biglia N, Peano E, Sgandurra P, Moggio G, Pecchio S, Maggiorotto F, et al. Body mass index (BMI) and breast cancer: impact on tumor histopatologic features, cancer subtypes and recurrence rate in pre and postmenopausal women. Gynecol Endocrinol 2013;29:263–7.
[31] Abusanad A, Alghamdi B, Alghamdi R, Khallaf R, Faisal K, Bishnaq R. The association of body mass index and adverse clinicopathological characteristics in non-metastatic breast cancer. J Fam Med Prim Care 2020;9:4190.
[32] Brouckaert O, Van Asten K, Laenen A, Soubry A, Smeets A, Nevelstreen I, et al. Body mass index, age at breast cancer diagnosis, and breast cancer subtype: a cross-sectional study. Breast Cancer Res Treat 2018;168:189–96.
[33] Blair CK, Wiggins CL, Nibbe AM, Storlie CB, Prossnitz ER, Royce M, et al. Obesity and survival among a cohort of breast cancer patients is partially mediated by tumor characteristics. NPJ Breast Cancer 2019;5:1–7.
[34] Lohmann AE, Soldera SV, Pimentel I, Ribnikar D, Ennis M, Amir E, et al. Association of obesity with breast cancer outcome in relation to cancer subtypes: a meta-analysis. JNCI J Natl Cancer Inst 2021;113:1465.
[35] Chan DSM, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol 2014;25:1901–14.
[36] Moon HG, Han W, Noh DY. Underweight and breast cancer recurrence and death: a report from the Korean Breast Cancer Society. J Clin Oncol 2009;27:5899–905.
[37] Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784–95.
[38] McCarty KS, Miller LS, Cox EB, Konrath J. Estrogen receptor analyses. Correlation of biochemical and immunohistochemical methods using monoclonal antireceptor antibodies. Arch Pathol Lab Med 1985;109:716–21.
[39] Balaton A,Le Doussal V, Arnould L, Barlier C, Bellocq JP, Ettore F, et al. Recommandations pour l'évaluation immunohistochimique des récepteurs hormonaux sur coupes en paraffine dans les carcinomes mammaires Mise à jour 1999. *undefined* (2008).
[40] Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.
[41] Kapoor E, Collazo-Clavell ML, Faubion SS. Weight gain in women at midlife: a concise review of the pathophysiology and strategies for management. Mayo Clin Proc 2017;92:1552–8.
[42] Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. Int J Cancer 2002;98:279–83.
[43] Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 2004;6:R149.
[44] Hellmann SS, Njor SH, Lynge E, von Euler-Chelpin M, Olsen A, Tjønneland A, et al. Body mass index and participation in organized mammographic screening: a prospective cohort study. BMC Cancer 2015;15:294.
[45] Mello-Thoms C. Mammographic breast density, body mass index, menopausal status, and breast cancer risk. JAMA Netw Open 2021;4.
[46] Vourtsis A, Berg WA. Breast density implications and supplemental screening. Eur Radiol 2018;29:1762–77.
[47] Engin A. Obesity-associated breast cancer: analysis of risk factors. Adv Exp Med Biol 2017;960:571–606.
[48] Simone V, D'avenia M, Argentiero A, Felici C, Rizzo FM, De Pergola G, et al. Obesity and Breast Cancer: Molecular Interconnections and Potential Clinical Applications. Oncologist 2016;21:404–17.
[49] Ayoub NM, Yaghan RJ, Abdo NM, Matalka II, Akhu-Zaheya LM, Al-Mohtaseb AH, et al. Impact of obesity on clinicopathologic characteristics and disease prognosis in pre- and postmenopausal breast cancer patients: a retrospective institutional study. J Obes 2019;2019:11.
[50] Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. CA Cancer J Clin 2017;67:378–97.
[51] Haakinson DJ, Leeds SG, Dueck AC, Gray RJ, Wasif N, Stucky CC, et al. The impact of obesity on breast cancer: a retrospective review. Ann Surg Oncol 2012;19:3012–8.
[52] Wang K, Wu YT, Zhang X, Chen L, Zhu WM, Zhang AJ, et al. Clinicopathologic and prognostic significance of body mass index (BMI) among breast cancer patients in Western China: a retrospective multicenter cohort based on Western China Clinical Cooperation Group (WCCCG). Biomed Res Int 2019;2019:1–14.
[53] Giles ED, Wellberg EA, Astling DP, Anderson SM, Thor AD, Jindal S, et al. Obesity and overfeeding affecting both tumor and systemic metabolism activates the progesterone receptor to contribute to postmenopausal breast cancer. Cancer Res 2012;72:6490–501.
[54] Tong Y, Zhu S, Chen W, Chen X, Shen K. Association of obesity and luminal subtypes in prognosis and adjuvant endocrine

treatment effectiveness prediction in Chinese breast cancer patients. Front Oncol 2022;12:1952.
[55] Jahanban Esfahlan R, Zarghami N, Esfahlan AJ, Mollazadeh M, Nejati K, Nasiri M. The possible impact of obesity on androgen, progesterone and estrogen receptors (ERα and ERβ) gene expression in breast cancer patients. Breast Cancer ((Auckl)) 2011;5:227.
[56] Enriori CL, Orsini W, del Carmen Cremona M, Etkin AE, Cardillo LR, Reforzo-Membrives J, et al. Decrease of circulating level of SHBG in postmenopausal obese women as a risk factor in breast cancer: reversible effect of weight loss. Gynecol Oncol 1986;23:77–86.
[57] Van Asten K, Slembrouck L, Olbrecht S, Jongen L, Brouckaert O, Wildiers H, et al. Prognostic value of the progesterone receptor by subtype in patients with estrogen receptor-positive, HER-2 negative breast cancer. Oncologist 2019;24:165–71.
[58] Dowsett M, Houghton J, Iden C, Salter J, Farndon J, A'hern R, et al. Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. Ann Oncol 2006;17:818–26.
[59] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. The Lancet 2011;378:771. https://doi.org/10.1016/S0140-6736(11)60993-8.
[60] De Schepper M, Vincent-Salomon A, Christgen M, Van Baelen K, Richard F, Tsuda H, et al. Results of a worldwide survey on the currently used histopathological diagnostic criteria for invasive lobular breast cancer. Mod Pathol 2022;35:1812–20. https://doi.org/10.1038/S41379-022-01135-2.
[61] Christgen M, Kandt LD, Antonopoulos W, Bartels S, Van Bockstal MR, Bredt M, et al. Inter-observer agreement for the histological diagnosis of invasive lobular breast carcinoma. J Pathol Clin Res 2022;8:191–205.
[62] Ellingjord-Dale M, Christakoudi S, Weiderpass E, Panico S, Dossus L, Olsen A, et al. Long-term weight change and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Epidemiol 2022;50:1914–26.
[63] Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627–35.
[64] Pimentel I, Lohmann AE, Goodwin PJ. Normal weight adiposity and postmenopausal breast cancer risk. JAMA Oncol 2019;5:150–1.
[65] Borruel S, Moltó JF, Alpanes M, Fernandez-Duran E, Alvarez-Blasco F, Luque-Ramirez M, et al. Surrogate markers of visceral adiposity in young adults: waist circumference and body mass index are more accurate than waist hip ratio, model of adipose distribution and visceral adiposity index. PLoS One 2014;9:e114112.
[66] Sun X, Casbas-Hernandez P, Bigelow C, Makowski L, Joseph Jerry D, Smith Schneider S, et al. Normal breast tissue of obese women is enriched for macrophage markers and macrophage-associated gene expression. Breast Cancer Res Treat 2012;131:1003–12.
[67] Vaysse C, Lømo J, Garred Ø, Fjeldheim F, Lofteroed T, Schlichting E, et al. Inflammation of mammary adipose tissue occurs in overweight and obese patients exhibiting early-stage breast cancer. NPJ Breast Cancer 2017;3:1.