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Original article

Impact of body mass index on overall survival in patients with metastatic breast cancer

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ABSTRACT

Background: High Body mass index (BMI) is a risk factor for breast cancer among postmenopausal women and an adverse prognostic factor in early-stage. Little is known about its impact on clinical outcomes in patients with metastatic breast cancer (MBC).
Methods: The National ESME-MBC observational cohort includes all consecutive patients newly diagnosed with MBC between Jan 2008 and Dec 2016 in the 18 French comprehensive cancer centers.
Results: Of 22 463 patients in ESME-MBC, 12 999 women had BMI data available at MBC diagnosis. Median BMI was 24.9 kg/m^2 (range 12.1–66.5); 20% of women were obese and 5% underweight. Obesity was associated with more *de novo* MBC, while underweight patients had more aggressive cancer features. Median overall survival (OS) of the BMI cohort was 47.4 months (95% CI [46.2–48.5]) (median follow-up: 48.6 months). Underweight was independently associated with a worse OS (median OS 33

Abbreviations: BC, breast cancer; BMI, body mass index; ESME, Epidemio-Strategy-Medical-Economical; HR, hormone receptor; MBC, metastatic breast cancer; PFS, progression free-survival; TNBC, triple negative breast cancer; OS, overall survival.

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Underweight
Obesity

months; HR 1.14, 95%CI, 1.02–1.27) and first line progression-free survival (HR, 1.11; 95%CI, 1.01; 1.22), while overweight or obesity had no effect.
Conclusion: Overweight and obesity are not associated with poorer outcomes in women with metastatic disease, while underweight appears as an independent adverse prognostic factor.

1. Background

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women in the world [1,2]. The mutual relationship between body mass index (BMI) and breast cancer (BC) risk and outcomes has been widely evaluated. Overweight or obesity is an independent predictor of BC risk in postmenopausal women, while it is protective before menopause [3–5]. BMI has also been demonstrated as an independent prognostic factor for overall survival (OS) in patients with early breast cancer (EBC) [6] [–] [8]. However, recent studies question the association between BMI and survival in EBC in certain BC subtypes [9–11]. Many hypotheses have been formulated and explored to explain these observations. Overweight or obesity may affect treatment dosing [12]. Multiple interactions between obesity-linked inflammation, adipose tissue activation or diet-induced metabolic changes and cancer risk or response to treatment have been described [13–15]. In patients with metastatic breast cancer (MBC), limited data are available regarding the impact of BMI on patients' outcome [16–21].

We therefore interrogated the UNICANCER Epidemio-Strategy-Medical-Economical (ESME)-MBC multicentre national retrospective prospectively maintained cohort, to assess the role of BMI on MBC survival outcomes. This cohort is an academic initiative launched by UNICANCER Group, the French network of cancer centers, to report exhaustive, high quality and centralised real-life data in MBC patients over the past ten years [22,23]. The primary objective of the present study was to evaluate the prognostic impact of BMI at MBC diagnosis on OS of women with metastatic breast cancer. The other objectives were to assess patient characteristics by BMI category, first-line progression-free survival (PFS), and impact of BMI on OS and PFS among the three major BC subtypes.

2. Materials and methods

2.1. ESME data platform and study population

The UNICANCER ESME-MBC data platform is a real-life retrospective, prospectively maintained database that collects exhaustive data of all consecutive patients, male or female, ≥18 years who have initiated their treatment for a MBC in one of 18 French Comprehensive Cancer Centers (FCCC) since January 1st, 2008. For the present study, we used the cohort recruited between this date and December 31, 2016. Data were collected until the cut-off date (October 13, 2018), death, or date of last contact in the centre, if lost to follow-up. Patients' demographics, cancer characteristics, pathology, outcomes and treatments were collected. Data were annually updated. The information gathered derived from the integration of data from medical records, multidisciplinary team meeting reports, hospitalization-related data and pharmacy-related data, as previously described [22]. Inclusion criteria for the present study (BMI cohort) were female, ≥ 18 years, and for whom BMI was available at diagnosis of the metastatic disease. Patients with phyllodes tumour, angiosarcoma and non-Hodgkin lymphoma, men and patients with MBC treated before January 2008 were excluded. The database and the data were described previously [22].

Four reported BMI categories were defined at the selection date for ESME (first treatment in FCCC) and according to the World Health Organization's definition: underweight (BMI < 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30.0 kg/m^2).

3. Objectives

Our primary objective was to evaluate whether BMI classified as 4 classes (underweight, normal weight, overweight and obesity) was an independent prognostic factor of OS in patients with MBC regardless of tumour subtype. Secondary objectives were (1) to evaluate whether BMI was an independent prognostic factor of OS in each BC subtype: hormone receptor-positive (estrogen and/or progesterone receptor positive) (HR) and HER2 negative (HR+/HER2-), HER2 positive (HER2+) and triple negative (HR-/HER2-or TNBC); (2) to assess whether BMI classes correlate with other patients and cancer characteristics and (3) to evaluate the potential impact of BMI on progression-free survival under first-line treatment (PFS1) in the overall study population according to the tumour subtype. All details about BC subtype assessment were previously published [23].

3.1. Ethical approval

The ESME research program was authorized by the French data protection authority (Registration ID 1704113 and authorization N°DE-2013.-117, NCT03275311) and is conducted by R&D Unicancer in accordance with current best practice guidelines [24,25]. The present analysis was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est II- 2015-79).

3.2. Statistical analysis

For descriptive analyses, the significance of the difference in the variables between different BMI groups was estimated using Chi-square tests or ANOVA tests. The primary endpoint, OS, was defined as the time between the date of diagnosis of metastatic disease and date of death (any cause) or censored to the date of latest contact. PFS1 was defined as the time from the initiation of this first-line treatment as time (months) and the date of first disease progression or death or censored to date of latest news. Disease progression was defined as appearance of new metastatic site, progression of existing metastasis, local or locoregional recurrence of the primary tumour, discontinuation of chemotherapy and/or targeted therapy due to metastatic progression (judged by the reference physician), or death from any cause.

We used the Kaplan–Meier method to estimate OS and PFS1, and log-rank tests to assess differences between BMI-subgroups. We used multivariable Cox proportional hazards models to identify prognostic factors of OS and PFS in the whole cohort, and to

calculate Hazard ratios (HR) and associated 95% confidence intervals (CI).

Variables of interest were: BMI at MBC diagnosis, classified as 4 classes (underweight, normal weight, overweight and obesity); age at diagnosis of MBC (<or ≥65 years); performance status (PS) (PS: 0, 1, 2–4); time to MBC, defined as the time from diagnosis of the primary cancer and diagnosis of MBC (<6 [6–24], 24 months); metastatic sites (bone only, bone and non-visceral metastases [skin, lymph nodes …], visceral metastases [liver, brain metastases] and others); number of metastatic sites (< 3, ≥3); MBC subtypes (HR+/HER2-, HER2+ and HR-/HER2-); symptom-versus screening-based diagnosis of MBC (defined as MBC diagnosed on symptoms versus MBC discovered based on the results of a blood or imaging test). All significant factors at 15% level in univariable analysis were included in multivariable analyses. The final models were considered to be reached when including only significant factors at a p = 0.05 significance level. All analyses were performed using R software, version 3.6.1.

4. Results

4.1. Characteristics and treatments of the overall population and BMI-subgroups

Among the 22 463 patients in the ESME-MBC cohort, 12 999 women had available baseline BMI data and constitute the whole BMI cohort (study population) (Fig. 1). Table 1 summarizes this cohort's patients and tumors' characteristics, as well as treatments, by BMI categories. The median age at initial cancer diagnosis and at MBC diagnosis was respectively 53 (range 16–103) and 60 years (range 19–103). The median time to MBC was 27.8 months (range 0.9 94.8 months). Median BMI at MBC was 24.9 kg/m^2 (range 12.1–66.5 kg/m^2). Six hundred thirty-seven patients (5%) were underweight; 6020 (46%) had normal weight; 3708 (29%) were overweight and 2634 (20%) were obese. As shown in Table 1, higher BMI categories were independently and inversely associated with symptom-based MBC diagnosis and positively associated with menopausal status, older age and more *de novo* MBC (all p < 0.001). Low BMI was associated with the presence of visceral metastases and a higher number of metastatic sites. Conversely, the frequency of bone-only metastases increased with increasing BMI (p < 0.001). Similarly, the prevalence of HR + HER2-subtype increased, while the frequency of TNBC subtype decreased with higher BMI.

4.2. Multivariable analysis for OS

The median follow-up of the whole BMI cohort was 48.6 months (range 0–126.1 months). The median OS of the cohort was 47.4 months (95% CI, 46.2–48.5) (Fig. 2A, Supplementary Table A.1). As shown in Fig. 2B, median OS was 33 months (95% CI, 29–40) in the underweight group, 47 months (95% CI, 45–49) in the normal weight group, 49 months (95% CI, 47–51) in the overweight group and 48 months in the obese group (95% CI, 45–51).

In the multivariable analysis, underweight (HR 1.14, 95%CI, 1.02–1.28) was an independent negative predictor for OS, together with PS 2–4 (HR, 3.01; 95% CI, 2.77–3.27), TNBC subtype (HR, 2.18; 95% CI, 2.02–2.36), age at MBC diagnosis ≥65 years (HR, 1.18; 95% CI, 1.12–1.25), presence of visceral metastases (HR, 1.90; 95% CI, 1.76–2.06), time to MBC 6–24 months (HR: 2.53; 95% CI, 2.34–2.74), and the number of metastatic sites ≥ 3 (HR, 1.45; 95% CI, 1.36–1.54) (Table 2). However, overweight or obesity had no impact on OS.

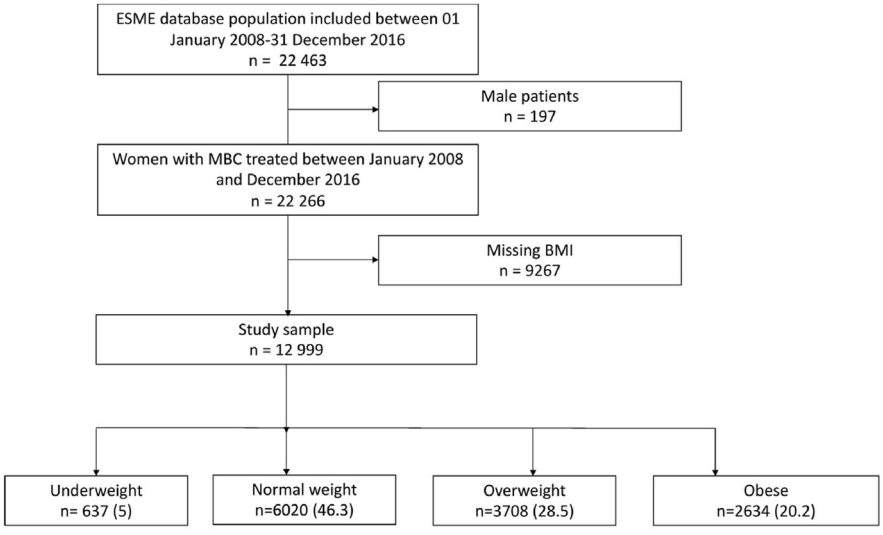
4.3. Multivariable analysis for first-line PFS

The median PFS1 of the whole cohort was 12.2 months (95% CI, 11.9–12.5). Underweight was associated with a significantly lower median PFS1 (9.2 months; 95%CI, 8.5–10.6) in comparison with the other 3 classes (normal weight: 12.2 (95%CI, 11.8–12.6), overweight: 12.7 (95%CI, 12.1–13.4) and obese: 12.4 (95%CI: 11.6–13.1) (Fig. 2C).

Multivariable analysis showed that underweight (HR, 1.11; 95% CI, 1.01; 1.22), the presence of visceral metastases (HR, 1.39; 95% CI, 1.31–1.47), metastatic sites ≥ 3 (HR, 1.28; 95% CI, 1.22–1.35), PS 2–4 (HR, 1.86; 95% CI, 1.74–1.99) and TNBC subtype (HR, 1.59; 95% CI, 1.5–1.69), were independent predictors of PFS1 (Supplementary Table A.2).

4.4. Multivariable analysis of OS among BC subtypes

When tested among each subtype, underweight was no longer an independent predictor of OS, although it tended to be so among



ESME, Epidemiological Strategy and Medical Economics; MBC: metastatic breast cancer

Fig. 1. Study flowchart. ESME, Epidemiological Strategy and Medical Economics; MBC: metastatic breast cancer.

Table 1
Patients, tumors characteristics at MBC diagnoses and treatments.

	Underweight (n = 637)	Normal weight (n = 6020)	Overweight (n = 3708)	Obesity (n = 2634)	P
Median age at MBC (years) (Q1–Q3 range)	58 (47–68)	58 (48–68.2)	61 (51–70)	60 (52–69)	<0.001
Age at MBC, n (%)	422 (66)	3962 (66)	2232 (60)	1680 (64)	<0.001
<65 years	215 (34)	2058 (34)	1476 (40)	954 (36)	
≥65 years					
Median BMI (kg/m^2) (Q1–Q3 range)	17.5 (16.7–18)	22.2 (20.8–23.6)	27.1 (26.0–28.3)	33.3 (31.2–36.4)	
Menopausal status at MBC, n (%)	123 (19)	1223 (20)	563 (15)	398 (15)	<0.001
Premenopausal	267 (42)	2694 (45)	1843 (50)	1386 (53)	
Post-menopausal	247 (39)	2103 (35)	1302 (35)	850 (32)	
Missing data					
Time to MBC (median, months) (Q1-Q3 range)	24.3 (0.7–81.4)	33 (1.1–103.5)	27.3 (0.8–92.1)	18.4 (0.7–77.2)	<0.001
Type of MBC[a], n (%)	228 (35.8)	1939 (32.2)	1389 (37.5)	1132 (42.9)	<0.001
De novo	406 (63.7)	4064 (67.5)	2311 (62.3)	1496 (56.8)	
Recurrent	3 (0.5)	17 (0.3)	8 (0.2)	6 (0.3)	
Missing data					
Mode of MBC diagnosis n (%)	355 (55.7)	3366 (55.9)	2125 (57.3)	1593 (60.5)	<0.001
Systematic	272 (42.7)	2529 (42)	1507 (40.6)	1012 (38.4)	
Symptomatic	10 (1.6)	125 (2.1)	76 (2)	29 (1.1)	
Missing data					
Performans Status, n (%)	125 (20)	1827 (30)	1080 (29)	661 (25)	<0.001
0	138 (22)	1366 (23)	883 (24)	691 (26)	
1	133 (21)	664 (11)	415 (11)	344 (13)	
2–4	241 (38)	2163 (36)	1330 (36)	938 (36)	
Missing data					
Breast cancer histological type n (%)	468 (73.5)	4454 (74.0)	2740 (73.9)	2043 (77.6)	0.012
Infiltrating ductal carcinoma	81 (12.7)	765 (12.7)	462 (12.5)	272 (10.3)	
Infiltrating lobular carcinoma	70 (11.0)	682 (11.3)	447 (12.1)	276 (10.5)	
Other	18 (2.8)	119 (2.0)	59 (1.6)	43 (1.6)	
Missing data					
Breast cancer subtype, n (%)	354 (56)	3566 (59)	2311 (62)	1633 (62)	0.001
HR + HER2-HER2+	131 (21)	1295 (22)	725 (20)	545 (21)	
TNBC	105 (16)	860 (14)	499 (13)	345 (13)	
Undetermined	47 (7)	299 (5)	173 (5)	111 (4)	
Metastatic sites, n (%)	130 (20)	1372 (23)	897 (24)	688 (26)	<0.001
Bone only	107 (17)	1105 (18)	663 (18)	462 (18)	
Bone and non-visceral metastases	236 (37)	2060 (34)	1102 (30)	716 (27)	
Visceral-only metastases	164 (26)	1483 (25)	1046 (28)	768 (29)	
Others					
Presence of visceral metastasis, n (%)	400 (63)	3543 (59)	2148 (58)	1484 (56)	0.015
Yes	237 (37)	2477 (41)	1560 (42)	1150 (44)	
No					
No of metastatic sites, n (%)	457 (72)	4684 (78)	2955 (80)	2081 (79)	<0.001
<3	180 (28)	1336 (22)	753 (20)	553 (21)	
≥3					
Received CT during 1st line, n (%)	416 (65)	4112 (68)	2460 (66)	1741 (66)	0.07
Yes	221 (35)	1908 (32)	1248 (34)	893 (34)	
No					
Received ET during 1st line, n (%)	258 (40)	2794 (46)	1791 (48)	1235 (47)	0.003
Yes	379 (60)	3226 (54)	1917 (52)	1399 (53)	
No					
Received targeted therapy during 1st line, n (%)	197 (31)	2073 (34)	1172 (32)	762 (29)	<0.001
Yes	440 (69)	3947 (66)	2536 (68)	1872 (71)	
No					

CT: chemotherapy: ET: endocrine therapy, HER2: Human Epidermal Growth Factor Receptor-2; HR: hormone receptor; MBC: metastatic breast cancer; PS: performance status; TNBC: triple-negative breast cancer.

[a] Type of MBC: MBC is considered '*de novo*' if the metastatic condition was detected at the same time as the primary cancer or within the following 6 months.

patients with TNBC (HR 1.24 [95% CI, 0.99–1.6]). Among TNBC patients, overweight however appeared slightly protective (HR 0.86 [95% CI, 0.75–0.98], p = 0.01). (Supplementary Tables A.3-A5).

Comparison of the study cohort's characteristics (N = 12 999) with those of patients with no BMI available (N = 9267).

Patients included in the present study (based on available BMI data) were diagnosed more recently (50.3% versus 32.2% diagnosed during years 2013–2016), were slightly younger (median age 60 years versus 62 years) and presented more frequently *de novo* MBC (36.2 vs 21.1%) as compared to women with no BMI available (Supplementary Tables A.6). Patients in the BMI cohort had better OS ((47.4 months [46.2–48.5] vs 31.5 [30.6–32.3]) and PFS1 (12.2 months [11.9–12.5] vs 9.3 months [9.0–9.7]) than those excluded.

5. Discussion

With more than 12 000 patients involved, the present study is the largest assessment yet conducted regarding the impact of BMI on survival outcomes among patients with metastatic breast cancer.

Underweight appears as an independent negative prognostic factor of both OS and first line PFS, while, in contrast, overweight

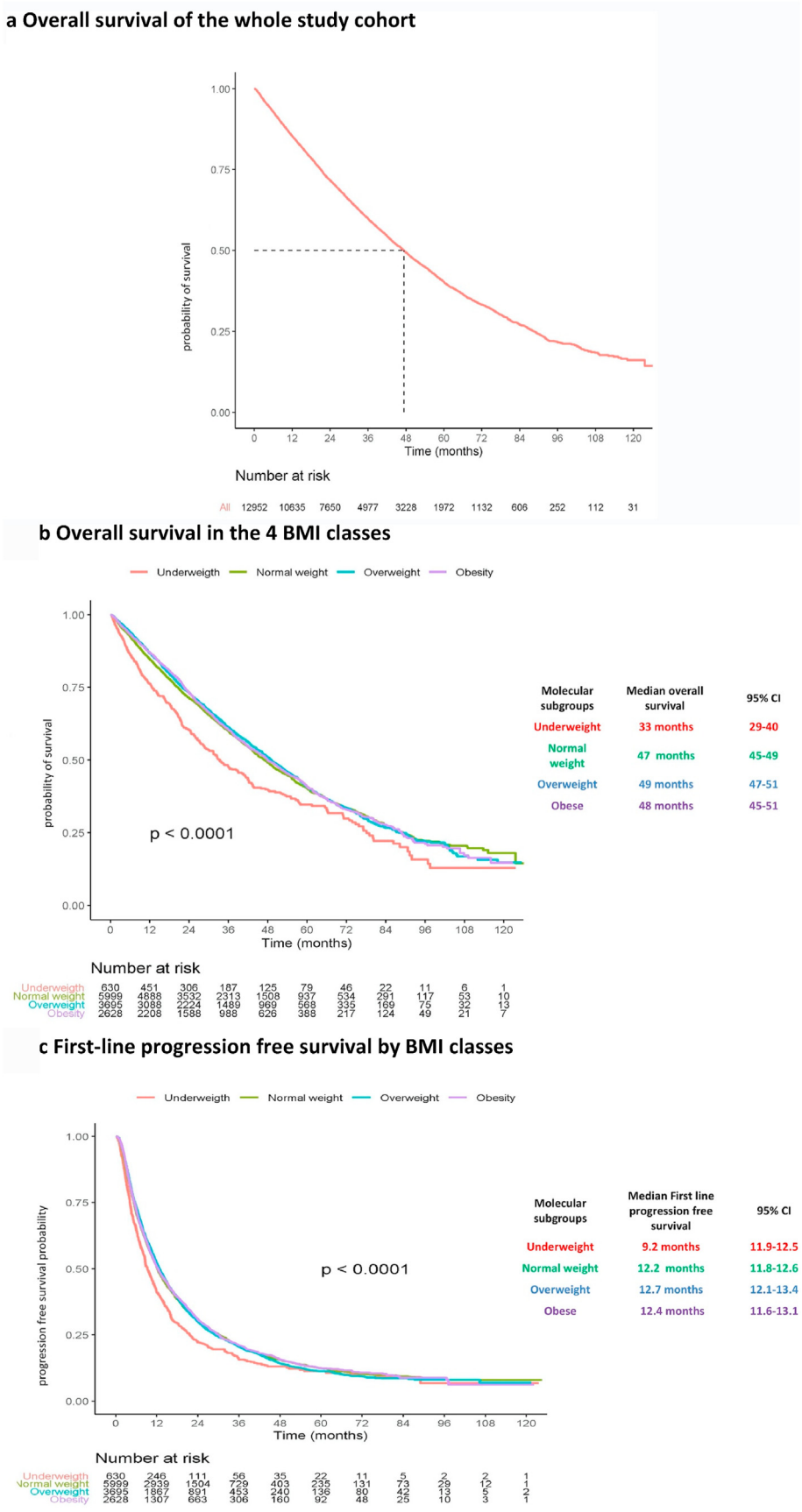


Fig. 2. Overall survival in the whole study population and by BMI classes; First-line progression free survival by BMI classes. Fig. 2a Overall survival of the whole study cohort. Fig. 2b Overall survival in the 4 BMI classes. Fig. 2c First-line progression free survival by BMI classes.

Table 2
Multivariable analysis for overall survival of the whole study population.

Factors	Categories	Number	HR	IC	p value
BMI 4 classes	Normal weight	6003	1		0.04
	Underweight	634	1.14	[1.02; 1.28]	
	Pre-Obesity	3700	0.97	[0.91; 1.02]	
	Obesity	2628	0.98	[0.91; 1.04]	
Age at MBC	<65 yrs	8275	1		All <0.001
	≥65 yrs	4690	1.18	[1.12; 1.25]	
Time to MBC	<6 months	4688	1		
	6–24 months	1476	2.53	[2.34; 2.74]	
	24–60 months	2227	1.66	[1.54; 1.78]	
	≥60 months	4574	1.04	[0.97; 1.11]	
Metastatic sites	Bone only	3077	1		
	Non visceral non bone only	2326	1.04	[0.95; 1.13]	
	Liver or brain	4112	1.90	[1.76; 2.06]	
	Other	3450	1.16	[1.08; 1.26]	
No. of organ sites	<3	10 146	1		
	≥3	2819	1.45	[1.36; 1.54]	
Breast cancer subtype	HR + HER2-	7844	1		
	HER2+	2691	0.61	[0.57; 0.66]	
	TNBC	1806	2.18	[2.02; 2.36]	
	Undetermined.	624	1.08	[0.97; 1.21]	
Performans status	PS 0	3687	1		
	PS 1	3071	1.42	[1.32; 1.53]	
	PS 2-4	1551	3.01	[2.77; 3.27]	
	Not available	4656	1.40	[1.31; 1.5]	
1st line CT	No	4250	1		
	Yes	8715	0.80	[0.75; 0.85]	
1st line ET	No	6903	1		
	Yes	6062	0.67	[0.63; 0.72]	
1st line TT	No	8767	1		0.07
	Yes	4198	0.95	[0.89; 1]	

and obese conditions were clearly not associated with prognosis. These results regarding high BMI among MBC patients are however consistent with those reported by Gennari et al. who evaluated the prognostic impact of BMI on OS and PFS in 489 patients with MBC receiving first-line chemotherapy [21]. Martel et al. did also not find an association between BMI and clinical outcomes in HER2-positive MBC [19]. In this retrospective cohort of 329 patients, there was no statistical difference in median PFS and OS between women with BMI <25 and women with BMI ≥25 ($p = 0.387$ and $p = 0.525$, respectively) [19]. Recently, Pizzuti et al. analysed data of 196 women with HER2-negative metastatic BC, treated with paclitaxel and bevacizumab and showed that BMI had no impact on survival particularly in the luminal subgroup [20]. In contrast to our report, these studies did however not distinguish underweight from normal weight patients. Two previous retrospective studies have reported a negative impact of obesity on outcomes in women with MBC but those series were both very small (96 and 55 patients respectively) [16,17]. Recently, Franzoi et al. evaluated the impact of BMI on outcomes in MBC patients treated with endocrine therapy (ET) combined to CDK 4/6 inhibitors. They found no PFS difference between BMI categories in any group [26].

Our results contrast with the reported adverse prognostic effect of overweight or obesity in patients with non-metastatic breast cancer. In a meta-analysis of 82 follow-up studies, obesity was associated with higher total mortality (relative risk (RR), RR 1.41 (95% CI 1.29–1.53)) and BC specific mortality (RR 1.35 (95% CI 1.24–1.47)) as compared to normal weight [8]. Furthermore, Ewertz et al. reported a 30-year follow-up of patients with EBC included in clinical trials within the Danish Breast Cancer Cooperative Group of whom 18 797 patients had available BMI [27]. The risk of developing distant metastases after 10 years was significantly increased by 46% and the risk of dying after 30 years was significantly increased by 38% for obese patients. Chemotherapy and endocrine therapy seemed also to be less effective after 10 or more years for obese patients [27].

While, in patients with early breast cancer, underweight is not associated with overall and BC specific survival [28], underweight at metastatic diagnosis seems to have a different significance and impact. In other cancers, underweight is also an adverse prognostic factor and has been associated with a higher risk of death [29]. To our knowledge, there are limited data about the impact of underweight on the long-term outcomes in MBC. A single previous study reported a better prognosis among 557 MBC women with a BMI <20 kg/m^2 compared with women with normal weight (HR = 0.52, 95% CI 0.31–0.87, $p = 0.013$). However, patients were included between 1999 and 2008 and treatment regimens were not considered. Furthermore, the definition of underweight used was not standard, with a cut-off at 20 kg/m^2 [30]. With a WHO definition-based cut-off at 18.5 kg/m^2, we showed that underweight was strongly associated with a worse prognosis as compared to other groups.

In the ESME MBC cohort, the availability of the BMI at MBC diagnosis varied mainly over time, and is much more frequently reported in recent years. BMI at primary cancer diagnosis was not available. Only 5% of patients in our cohort were underweight, which is in line with data in localised BC cohorts such as the national CANTO cohort [31]. In our study, underweight women had more visceral metastases and more metastatic sites. These two adverse prognotic factors may be associated with a lower BMI because of a poorer general condition and/or a marker of disease aggressiveness. However, no causal relationship between low BMI and outcomes, in a way or the other, can be clearly evidenced from our study. Of note, underweight's effect appeared however independent of all other risk factors. Treatments received did not differ between BMI categories.

The strengths of the present study are that it is based on a large, high quality updated nationwide, multicentre cohort of patients with MBC and for whom complete information on characteristics,

treatment and clinical outcomes are available.

One limitation of our study is that the ESME MBC cohort is retrospective, with no systematic data on evolution of weight over time, weight loss before diagnosis nor tolerance and safety data. As well, BMI and performance status are not available at MBC diagnosis in the entire ESME population (9267 patients were excluded for missing BMI). No data regarding body composition are available, although that could be of importance. Indeed, BMI alone cannot estimate the women's muscle mass and adiposity, therefore precluding direct explanation of our results in the underweight population. A large literature has recently assessed the adverse effect of sarcopenia and under-nutritional states in patients with advanced cancer [32–34]. In women with early BC and MBC, an emerging area of research is focusing on body composition rather than overall body weight [35]. Sarcopenia, or low skeletal muscle mass and strength, emerge as an independent prognostic factor in EBC [32,36] as well as MBC in few studies [37–39]. Caan et al. concluded that patients with sarcopenia had a higher overall mortality in a large cohort of non-MBC (n = 3248) [40]. In MBC resistant to anthracycline and/or taxane treatment, Prado et al. reported that sarcopenia was a significant predictor of toxicity and time to tumour progression in patients treated with capecitabine [39]. The discrepancy between the effect of obesity among women with early and metastatic cancers may be related to the already described "obesity paradox" (high BMI is associated with significantly longer cancer-specific survival in individuals with advanced disease) [41,42]. A small recent prospective study suggested that being overweight could improve OS in patients with metastatic BC receiving chemotherapy (n = 82) [43]. Of note, in ESME, overweight patients with the worse subtype (TNBC) indeed had better OS than normal weight ones (HR 0.86 [95% CI, 0.75–0.98], p = 0.01). Another explanation is that BMI is an imprecise measure of body composition. Body composition parameters might help to explain the obesity paradox because in high BMI population, low muscle mass was associated with higher risk of recurrence, overall and cancer-specific mortality [44,45]. Unfortunately we did not have data on cancer-related cachexia in this cohort (muscle strength …). The differential pharmacokinetics of targeted agents in overweight/obese or underweight patients could be also one possible underlying explanation for different outcomes [46]. However, this study was not designed to provide this type of information.

6. Conclusion

The present study identifies underweight (5% of this MBC patients' population) as an adverse independent prognostic factor for OS and first line PFS in patients with metastatic breast cancer. Obesity and overweight did however not predict for survival, except among patients with TNBC, where obesity appeared slightly protective. Because of limitations such as reverse causality and treatment selection bias, it is not possible to conclude that the association showed between underweight and outcome is causal. Underweight conditions should however be the focus of clinical attention at the time of MBC diagnosis. They should be explored, and potentially analysed separately in cohort studies. Targeted interventions could be prompted in this subgroup, including nutritional management and/or exercise intervention. Interventions against sarcopenia and undernutrition should involve dieticians and nutritionists. More specifically for sarcopenia, physiotherapists and fitness counsellors in management of muscle loss would be needed.

Contributors

KS and SD: conception and design. MR, MC and CC: data acquisition, interpretation and statistical analysis. VD, PEH, EB, VD, AM, AP, AMR, AG, JMF, TP, EG, LU, MD, FD, CJ, SL, ML, PC, LV and AS: data acquisition, interpretation. KS, SD, ED, MS: interpretation, writing of the first draft of the manuscript. All authors contributed to the manuscript, critically revised the manuscript, and approved the final version.

BMI: body mass index; HR: hazard ratio; MBC: metastatic breast cancer; CI: confidence interval; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple negative breast cancer.

Declaration of Competing interest

V.D reports advisory boards from Roche, Genentech, Lilly, Pfizer, Astra Zeneca, MSD, Daiichi Sankyo and Seattle Genetics.

PE-H reports research funding from Pfizer, Novartis

E.B receive honoraria or consultation fees: AstraZeneca, BMS, Celgene, Clinigen, G1 Therapeutics, Hospira, Janssen, Mylan, OBI Pharma, Pfizer, Puma, Roche, Samsung; Receipt of grants/research supports: Amgen, HalioDX (Qiagen/Ipsogen), TEVA (Cephalon); Travel support: AstraZeneca, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz.

A.G reports travel expenses, accommodation and registration meeting from Astra Zeneca, Roche, Pfizer, Novartis.

P.C reports grants form Pfizer and Novartis, personal fees from Pfizer and Lilly, non-financial support from Pfizer.

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E.D reports travel expenses from Pfizer, Novartis and Amgen and boards from Novartis and Pfizer.

The other authors declare that they have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.11.014.

18 Participating French Comprehensive Cancer Centers (FCCC): I. Curie, Paris/Saint-Cloud, G. Roussy, Villejuif, I. Cancérologie de l'Ouest, Angers/Nantes, C. F. Baclesse, Caen, ICM Montpellier, C. L. Bérard, Lyon, C. G-F Leclerc, Dijon, C. H. Becquerel, Rouen; I. C. Regaud, Toulouse; C. A. Lacassagne, Nice; Institut de Cancérologie de Lorraine, Nancy; C. E. Marquis, Rennes; I. Paoli-Calmettes, Marseille; C. J. Perrin, Clermont Ferrand; I. Bergonié, Bordeaux; C. P. Strauss, Strasbourg; I. J. Godinot, Reims; C. O. Lambret, Lille.

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Ethics approval and consent to participate

The ESME research program was authorized by the French data protection authority (Registration ID 1704113 and authorization N°DE-2013.-117, NCT03275311) and conducted by R&D Unicancer in accordance with current best practice guidelines [24,25]. The present analysis was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est II- 2015-79).

Consent for publication

All authors provided consent for publication.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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