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Trajectories of cognitive performance over five years in a prospective cohort of patients with breast cancer (NEON-BC)

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ABSTRACT

Purpose: To identify trajectories of cognitive performance up to five years since diagnosis and their predictors, in a cohort of patients with breast cancer (BCa).
Methods: A total of 464 women with BCa admitted to the Portuguese Institute of Oncology, Porto, during 2012, were evaluated with the Montreal Cognitive Assessment (MoCA) before any treatment, and after one, three and five years. Probable cognitive impairment (PCI) at baseline was defined based on normative age- and education-specific reference values. Mclust was used to define MoCA trajectories. Receiver Operating Characteristic curves were used to assess the predictive accuracy for cognitive trajectories.
Results: Two trajectories were identified, one with higher scores and increasing overtime, and the other, including 25.9% of the participants, showing a continuous decline. To further characterize each trajectory, participants were also classified as scoring above or below the median baseline MoCA scores. This resulted in four groups: 1) highest baseline scores, stable overtime (0.0% with PCI); 2) lowest baseline scores (29.5% with PCI); 3) mid-range scores at baseline, increasing overtime (10.5% with PCI); 4) mid-range scores at baseline, decreasing overtime (0.0% with PCI). Adding the change in MoCA during the first year to baseline variables significantly increased the accuracy to predict the downward trajectory (area under the curve [AUC] = 0.732 *vs.* AUC = 0.841, $P < 0.001$).
Conclusion: Four groups of patients with BCa with different cognitive performance trends were identified. The assessment of cognitive performance before treatments and after one year allows for the identification of patients more likely to have cognitive decline in the long term.

1. Introduction

Different cancer treatments, including chemotherapy [1,2], hormone therapy [3–5], radiotherapy [6], immunotherapy [7] and surgery [8], as well as cancer itself [9], have been described as possible causes of cognitive changes. Cognitive impairment has been estimated to affect up to 30% of patients before chemotherapy, up to 75% during treatment and up to 35% several years after the completion of treatment [10]. Although cancer-related cognitive impairment may be milder compared to cognitive impairment due to stroke, traumatic brain injury or dementia, it was shown to have a sizable impact on the daily life of oncologic patients, namely patients with breast cancer [11,12]. However, studies on the frequency of cognitive impairment among patients with cancer have yielded heterogenous results, which largely reflect methodological

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differences [13,40], namely regarding the validity of the instruments used and their coverage of cognitive domains, the criteria used to define cognitive impairment, and the type of comparison groups included.

Most of the studies have a post-treatment evaluation only or pre- and post-treatment assessments within a short period of time, which do not inform about the reversibility or persistence of cognitive impairment. The definition of trajectories over long periods and the early identification of their determinants are particularly important in cancers with an increasing number of long-term survivors, such as breast cancer [15–17]. Cancer treatments may affect cognitive performance during the first year after breast cancer diagnosis, with deficits persisting for longer periods, or being reversed following the end of treatment, due to compensatory or adaptative mechanisms. Cognitive decline may also occur in the longer term, due to a delayed effect of the initial treatments, as well as due to longer treatments, such as hormone therapy.

Therefore, this study aimed to identify trajectories of cognitive performance up to five years since diagnosis and their predictors, in a cohort of patients with breast cancer submitted to surgery, and to local and systemic adjuvant treatments.

2. Methods

2.1. The NEON-BC cohort

This study is based on the NEON-BC cohort, which was designed to investigate the neurological complications of breast cancer, and is previously described in detail [18]. Briefly, this is a prospective cohort assembled in 2012. Women recently diagnosed with breast cancer and admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal, were consecutively invited to participate if they did not have a history of chemotherapy or radiotherapy treatment for another primary cancer, had no previous breast surgery, and were able to understand the purpose of the study. Those who presented a Montreal Cognitive Assessment (MoCA) score lower than 17 or 16, if they were aged 65 years or more, were excluded because they were considered less likely to understand the study and to complete the questionnaire evaluations [19]. A total of 506 participants were assessed at baseline, before any cancer treatment; 503, 475 and 466 were evaluated at one, three and five years after diagnosis, respectively.

2.2. Evaluation of the participants

Socio-demographic characteristics and lifestyles were assessed in face-to-face interviews using a structured questionnaire. Clinical characteristics and treatment details were abstracted from clinical files. Staging was defined by the AJCC TNM 7th edition classification [21]. Breast cancer subtypes were based on the information from medical files regarding immunohistochemistry and in situ hybridization-based biomarkers, namely hormone receptors (HR) (estrogen receptors and progesterone receptors present in more or less than 1% of the cells) and human epidermal growth factor receptor (HER2), and were classified in HR-positive/HER2-negative (HR+/HER2-), HER2-positive (HER2+), and triple negative (HR-negative/HER2-negative). Validated questionnaires were used to assess patient-reported outcomes, namely anxiety and depression (Hospital Anxiety and Depression Scale [HADS] [20,21]), and sleep quality (Pittsburg Sleep Quality Index [PSQI] [22]). At each wave, cognitive performance was evaluated with MoCA (Portuguese version 7.1), by trained researchers; all participants except two were evaluated with MoCA in all follow-up assessments [18]. This cognitive test was designed as a screening tool to detect mild cognitive impairment by assessing eight cognitive domains: executive function; visuospatial ability; short-term memory; language; attention; concentration; working memory; and temporal and spatial orientation. Its score ranges from 0 to 30. It has good reliability, sensitivity and specificity to detect mild cognitive impairment [23,24]. Participants with a MoCA score below two standard deviations of age- and education-specific distributions from normative data [19] were classified as having probable cognitive impairment (PCI).

2.3. Statistical analysis

A total of 464 participants with a MoCA score in the four evaluations were included in the present analysis; these were not significantly different from those excluded (n = 42), regarding age (mean, 54.5 *vs.* 57.4, P = 0.103), education (mean, 7.7 *vs.* 6.9, P = 0.227) and cancer stage (stage 0/I, 54.7% *vs.* 39.0%; stage II, 30.2% *vs.* 39.0%; stages III/IV, 15.1% *vs.* 22.0%, P = 0.147).

The nlme package of the R Statistic Software [25] was used to fit a linear mixed-effects model with the fixed-effect of age and education as continuous variables (plus education as a quadratic term), and time as a random variable. An adjusted MoCA score (aMoCA) was computed as follows: aMoCA = raw MoCA − ($coefficient_{age}$ x age + $coefficient_{education}$ x education + $coefficient^2_{education}$ x $education^2$). Mclust [26] was used to obtain model-based clusters of the trends in the aMoCA score over the five years and the decision regarding the number of clusters was based on the Bayesian Information Criteria (Supplementary material, Fig. 1).

Data are presented as counts and proportions. Proportions were compared using the Chi-square test. The association between variables measured at baseline or within the first year of follow-up and the five-year cognitive trajectories was estimated with Odds Ratios (ORs) and their respective 95% confidence intervals (CI), computed using multivariable logistic regression; the variables included in the models are described in the footnotes of Fig. 2. The predictive accuracy of the variables significantly associated with the trajectories was further assessed using Receiver Operating Characteristic curves (ROC) and the corresponding areas under the curve (AUC) were compared [27].

Statistical analysis was conducted using R, version 3.3.1 (R Core Team, Vienna, Austria) and Stata, version 15.1 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Characterization of the cohort overtime

At baseline, median age was 54 years, a total of 42% of the women had less than five years of education and 29.4% had more than 10 years. Most tumours were classified as stage 0/I (54.7%), and stages II, III and IV represented 30.2%, 14.7% and 0.4% of the cases, respectively. The most frequent breast cancer subtype was HR+/HER2- (77.0%), followed by HER2+ (14.7%) and triple negative (8.3%) (Supplementary material, Table 1).

Only 15 (3.2%) women were treated with surgery as the single treatment. Regarding the treatments performed during the first year after diagnosis, 36.2% of the women received a combination of chemotherapy, radiotherapy and hormone therapy, and 21.9% were treated with radiotherapy and hormone therapy (Supplementary material, Table 2).

3.2. Identification of the cognitive trajectories

Two trajectories of cognitive performance were identified based on the aMoCA score: 1) the *upward trajectory*, with higher scores and increasing overtime, and 2) the *downward trajectory*, which

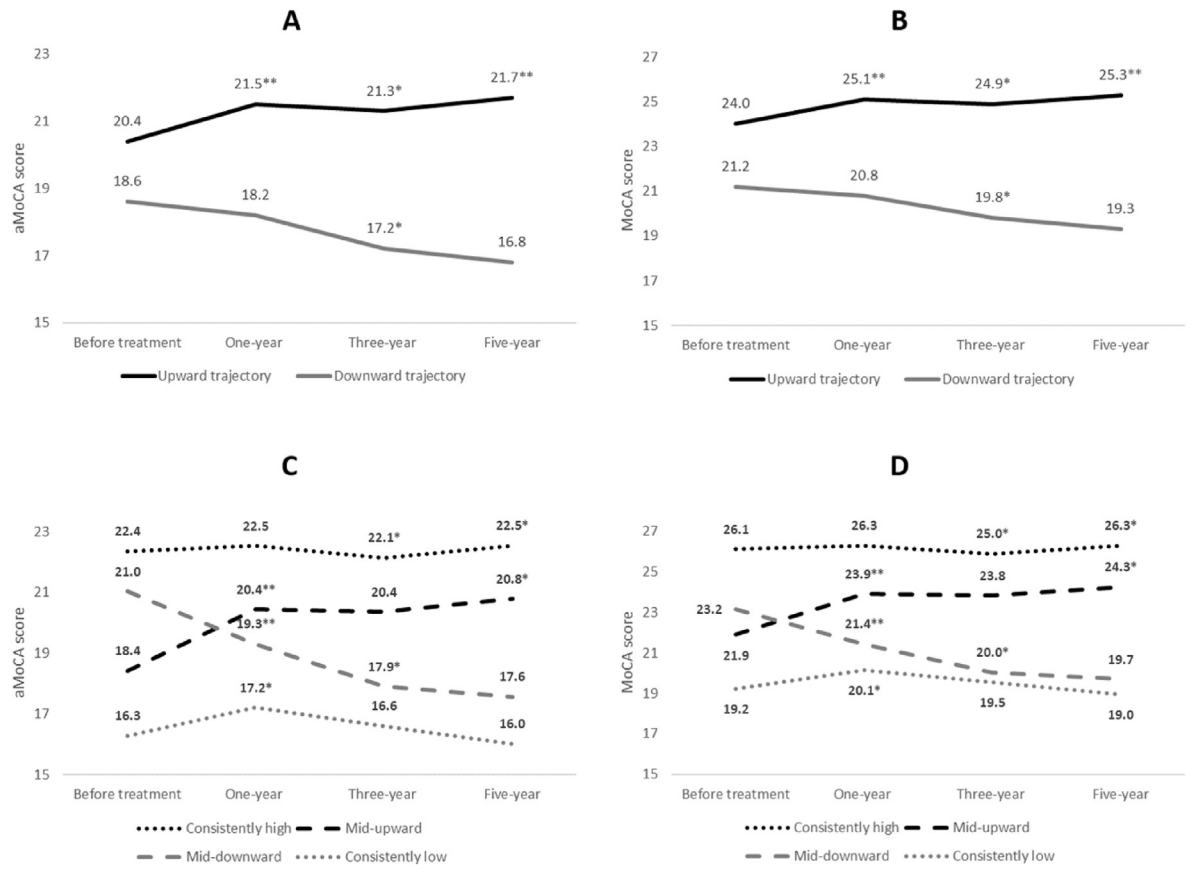

Fig. 1. Cognitive trajectories since before treatment to five years after diagnosis, represented with the raw score of the Montreal Cognitive Assessment (MoCA) and with its age- and education-adjusted value (aMoCA score). Graphs A and B: the two model-based trajectories, Upward and Downward; Graphs C and D: patterns of cognitive performance in the groups Consistently high - women of the Upward trajectory with a baseline MoCA score > median; Mid-upward - women of the Upward trajectory with a baseline MoCA score ≤ median; Mid-downward - women of the Downward trajectory with a baseline MoCA score > median; Consistently low - women of the Downward trajectory with a baseline MoCA score ≤ median. *P < 0.01 and **P < 0.001, for the change between consecutive evaluations, within each trajectory.

included 25.9% of the participants, and showed a continuous decline (Fig. 1A and B). To further characterize each trajectory, participants were also classified in each trajectory as scoring above or below the median of the baseline MoCA scores within each trajectory. The trajectories in each of the four groups obtained are depicted in Fig. 1C and D, and may be described as follows: 1) the *consistently high* group (n = 172) had the highest baseline scores, stable overtime (0.0% with PCI); 2) the *consistently low* group (n = 61) had the lowest scores overtime (29.5% with PCI); 3) the *mid-upward* group (n = 172) had mid-range scores at baseline, increasing overtime (10.5% with PCI); 4) the *mid-downward* group (n = 59) had mid-range scores at baseline, decreasing overtime (0.0% with PCI). All groups presented an increase in cognitive performance beween the baseline and the one-year evaluation (not statistically significant for the *consistently high* trajectory), except the *mid-downward* group that presented the highest decrease in the first year after diagnosis. The age, education, MoCA scores over the five years, and changes in MoCA scores in each of these groups are presented in supplementary table 3. In the *mid-downward* group, the mean changes (95%CI) in the MoCA score from baseline to the one-, three- and five-year evaluations were −1.7 (−2.5, −1.0), −3.1 (−3.9, −2.3) and −3.5 (−4.4, −2.6), respectively.

Fig. 2 depicts the ORs for the association between variables measured at baseline and during the first year, and the five-year *downward trajectory*. Significant associations were observed for age (≥65 *vs.* <50 years: OR = 2.34, 95%CI, 1.32–4.18), education (>12 *vs.* ≤4 years: OR = 0.31, 95%CI, 0.14–0.70), baseline MoCA score (per one point increase: OR = 0.77, 95%CI, 0.70–0.84), change in MoCA score during the first year (per one point increase: OR = 0.58, 95%CI, 0.51–0.66), consumption of psycholeptic drugs (OR = 1.67, 95%CI, 1.07–2.59), and depression but only at the one-year evaluation (OR = 2.64, 95%CI, 1.48–4.66).

Fig. 3 depicts the ROC curves for age, education, baseline and one-year MoCA scores, variation in the MoCA score during the first year of follow-up, and combinations of these variables to classify participants as pertaining to the *downward* or the *upward* trajectory. When considering all baseline predictors, the AUC was 0.732, and increased significantly when adding the one-year MoCA score (AUC = 0.841) or the change in MoCA during the first year (AUC = 0.841) to the model. The AUC for the consumption of psycholeptic drugs at baseline was 0.651 (95%CI: 0.597, 0.705), and it did not increase the accuracy of the remaining models. PCI at baseline was a predictor of cognitive trajectories with a low AUC of 0.549, and did not significantly improve the models based on age, education, and MoCA scores at baseline and at the one-year evaluation.

Fig. 4 depicts the distribution of the probability of belonging to the *downward* trajectory, as predicted by the model including only baseline variables (A) or baseline variables and variation in the MoCA score during the first year (B), with the latter showing a much smaller overlap between individuals in the *upward* and *downward* trajetories. This translates into an increased ability of the model including the variation in the MoCA score during the first year to identify women in the *downward* trajectory; the positive

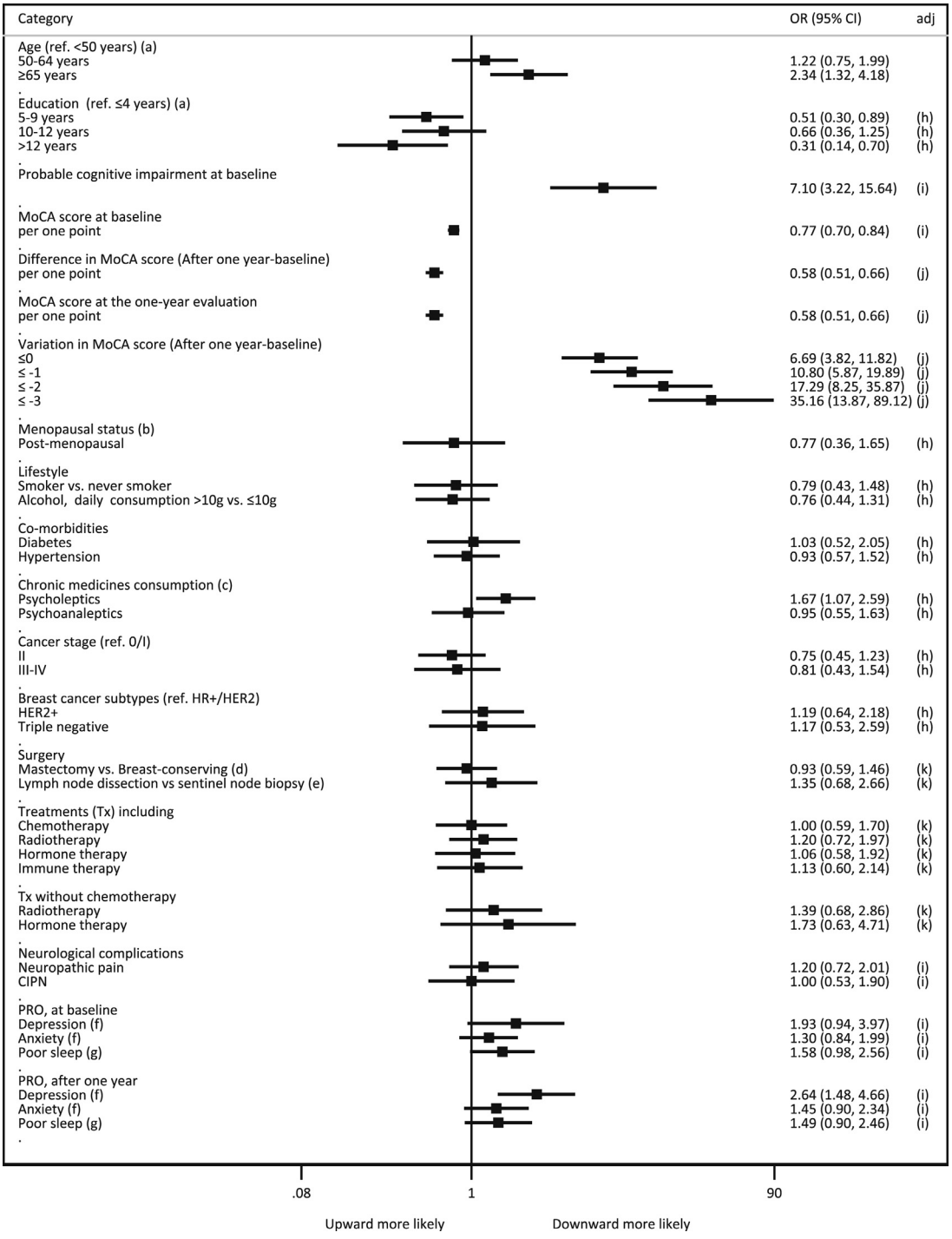

Fig. 2. Association of cognitive performance at baseline and its variation after one year, socio-demographic characteristics of the patients, lifestyle, co-morbidities, clinical characteristics of the tumor, treatments, neurological complications and patient-reported outcomes (PRO) with cognitive trajectories - *Downward vs.Upward*. CIPN, chemotherapy-induced peripheral neuropathy; PRO, patient-reported outcomes; Tx, treatments (a) Categories of age and education as they are used in the classification for cognitive impairment based on normative data. (b) When menopausal status was not specified, all women with at least 60 years of age, women who underwent a bilateral oophorectomy and those with an intact uterus and being amenorrheic for 12 or more consecutive months prior to the diagnosis in the absence of alternative pathological or physiological cause and follicle stimulating hormone and serum estradiol levels within the laboratory's reference ranges were classified as postmenopausal, or otherwise as premenopausal. (c) According to drug classification of the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index). (d) One patient only performed axillary surgery. (e) Patients who had both lymph node dissection and sentinel lymph node biopsy are reported as lymph node dissection. https://www.whocc.no/atc_ddd_index (f) Depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale. (g) Poor quality of sleep was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index. (h) Adjusted for age. (i) Adjusted for age, education. (j) Adjusted for age, education and baseline MoCA score. (k) Adjusted for age, education and cancer stage.

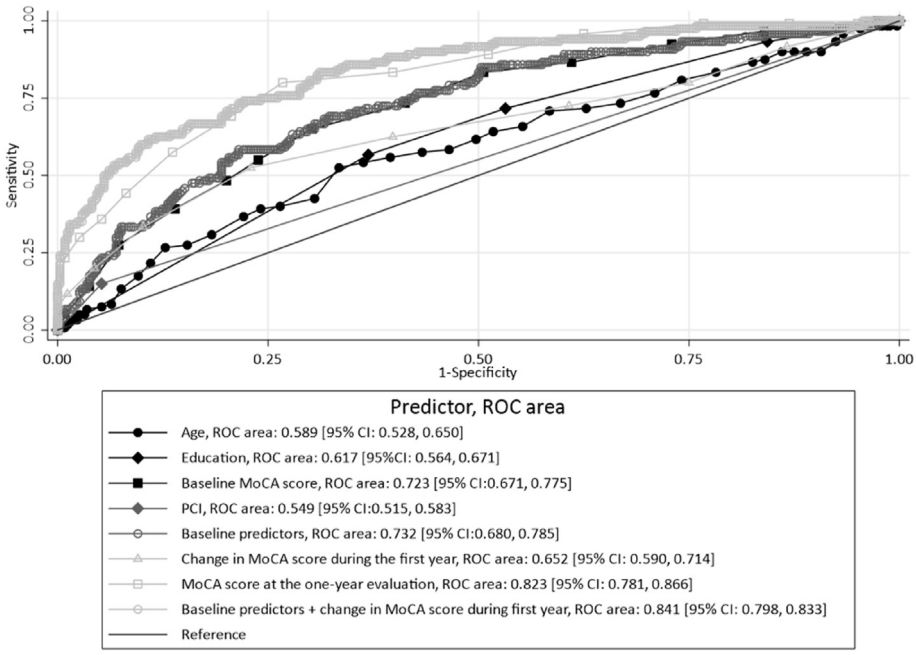

Fig. 3. Receiver operating characteristic curves of predictive models of the downward trajectory in women with breast cancer. AUC, Area Under the Curve; MoCA, Montreal Cognitive assessment; PCI, Probable cognitive impairment at the baseline evaluation defined as scoring below two standard deviations of the age- and education-specific distribution from normative data; ROC, Receiver Operating Characteristic. Age in years, education in four categories (≤4, 5–9, 10–12, >12 years); Baseline predictors: age, education and baseline MoCA score. AUC(model with age)≠AUC(model with education), P = 0.378. AUC(model with age)≠AUC(model with PCI), P = 0.319. AUC(model with education) ≠AUC(model with baseline MoCA score), P < 0.001. AUC (model with baseline MoCA score)≠AUC(model with baseline predictors), P = 0.295. AUC (model with baseline predictors) ≠AUC(model with baseline predictors + change in MoCA score during the first year), P < 0.001. AUC(model with MoCA score at the one-year evaluation)≠AUC(model with baseline predictors + change in MoCA score during the first year), P = 0.102.

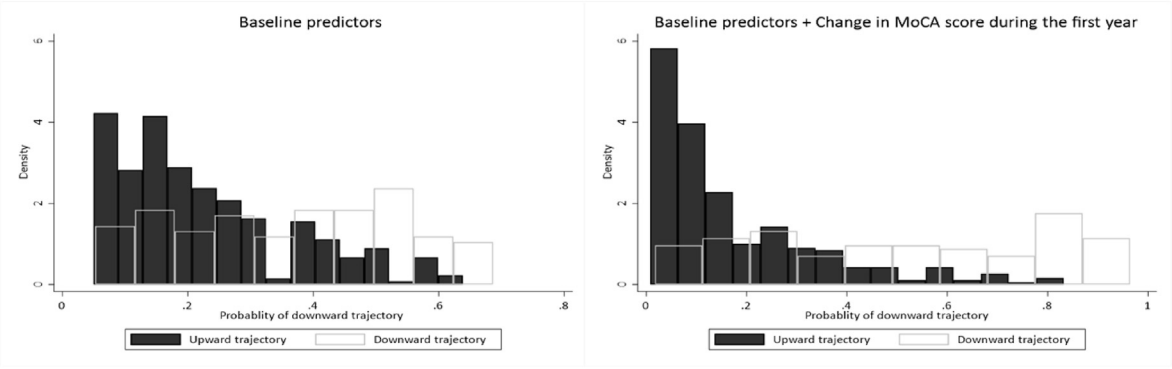

Fig. 4. Distribution of the probabilities of belonging to the *downward* trajectory estimated by the model based on the baseline predictors age, education (≤4, 5–9, 10–12, >12 years) and Montreal Cognitive Assessment (MoCA) score, and by the same model plus the variation in the MoCA score during the first year (score at the one-year evaluation - baseline score).

likelihood ratios ranged between 5.6 and 80.5 when the cut-off was set at estimated probabilities between 40% and 80% (Table 1).

4. Discussion

D*ownward* and *upward* cognitive trajectories were identified among women with breast cancer followed for five years. Just over one-quarter of the participants were in the *downward* trajectory, which included women with consistently low cognitive tests, as well as those who had a worsening performance overtime. The *upward* trajetory included both patients with consistently high scores and those who improved their performance. A model including age, education and baseline MoCA had a moderate accuracy to predict the five-year trajectory, which was significantly improved when further considering the variation in MoCA during the first year.

Our results show that cognitive impairment before breast cancer treatments detected using MoCA does not necessarily predict a *downward* cognitive trajectory as approximately half of these women recovered at follow-up evaluations. Cognitive performance also increased from baseline to the one-year evaluation in most of the women. Distress due to cancer diagnosis may have negatively affected cognitive performance at the baseline evaluation [28], and has been shown to be lower one year after breast cancer diagnosis [29]. Accordingly, in our cohort, we observed that the proportion of women with anxiety decreased significantly from baseline to the one-year evaluation. On the other hand, an increase in the MoCA score after one year was previously described in an elderly general

Table 1
Predictive models of the *downward* trajectory: sensitivity, specificity and likelihood ratios.

Model A: Baseline predictors							Model B: Baseline predictors + change in the MoCA score during the first year						
Pr %	Women predicted to be in the *downward* trajectory in the		Sensitivity %	Specificity %	LR+	LR-	Pr %	Women predicted to be in the *downward* trajectory in the		Sensitivity %	Specificity %	LR+	LR-
	upward trajectoy (n = 344)	*downward* trajectory (n = 120)						*upward* trajectoy (n = 344)	*downward* trajectory (n = 120)				
1	344	120	100.0	0	1.0	–	1	340	120	100.0	1.2	1.0	–
5	343	120	100.0	0.3	1.0	0.0	5	257	117	97.5	25.3	1.3	10.1
10	287	114	95.0	16.6	1.1	0.3	10	188	112	93.3	45.4	1.7	6.8
20	167	95	79.2	51.5	1.6	0.4	20	105	97	80.8	69.5	2.7	3.6
30	94	72	60.0	72.6	2.2	0.6	30	67	81	67.5	80.5	3.5	2.5
40	49	53	44.2	85.8	3.1	0.7	40	37	72	60.0	89.2	5.6	2.2
50	24	35	29.2	93.0	4.2	0.8	50	21	61	50.8	93.9	8.3	1.9
60	3	8	6.7	99.1	7.7	0.9	60	13	47	39.2	96.2	10.4	1.6
70	0	0	0.0	100.0	–	1.0	70	5	41	34.2	98.6	23.6	1.5
80	0	0	0.0	100.0	–	1.0	80	1	28	23.3	99.7	80.5	1.3
90	0	0	0.0	100.0	–	1.0	90	0	9	7.5	100.0	–	1.1
95	0	0	0.0	100.0	–	1.0	95	0	2	1.7	100.0	–	1.0
99	0	0	0.0	100.0	–	1.0	99	0	0	0.0	100.0	–	1.0

MoCA, Montreal Cognitive Assessment; Pr, probability; LR+, positive likelihood ratio; LR-, negative likelihood ratio.
Model A, based on the baseline predictors age, education (≤4, 5–9, 10–12, >12 years) and MoCA score, and model B, based on the same baseline predictors plus the variation in the MoCA score during the first year (score at the one year evaluation - baseline score).

population and may be explained by a practice effect [30], which may be defined as a change or improvement that results from practice or repetition of task items or activities [31]. Practice effect may be due to deliberate rehearsal, incidental learning, procedural learning, changes in an examinee's conceptualization of a task, shift in strategy, or increased familiarity with the test-taking environment and/or paradigm (i.e., "test-wiseness") [32], and it represents a source of measurement error. However, it may also be informative, since practice effect is largely absent in patients with Alzheimer's disease and it may predict cognitive outcomes in amnestic mild cognitive impairment [33].

Among women in the *mid-downward* group, a decrease of at least two points in the MoCA score, which could be considered a clinically significant difference [34], was observed in more than half of the women after one year and in all except one after five years of follow-up. These women were older and less educated, in accordance with older age and lower education being associated with a pathologic progressive deterioration of cognition, such as mild cognitive impairment and dementia [35,36]. Several other sociodemographic characteristics of the participants, lifestyle data and clinical characteristics at baseline were tested but none except age, education and consumption of psycholeptics drugs were associated with the trajectories. Psycholeptics drugs, namely benzodiazepines may increase the risk of cognitive decline [37]. Although chemotherapy was not associated with the *downward* trajectory, we have previously reported a statistical association between chemotherapy and incident cognitive impairment after one year of follow-up in the NEON-BC cohort, which was only observed among women with no anxiety at baseline [38]. The potential negative effect of antineoplasic drugs in cognitive function may be milder and transient in some patients, and chronic in others. Therefore, patients who received chemotherapy and had mild or transient cognitive decline may not be included in the worse cognitive trajectories, which could explain the absence of an association between chemotherapy and long-term cognitive decline. Also, the overall toxicity level of chemotherapy treatments may have decreased in the last two decades, due to the use of different drugs and doses, as well as a better mangement of toxic effects, and women of the NEON-BC cohort may have not been exposed to toxicity levels that would have an impact on cognitive function. The chemo brain hypothesis may not hold considering the current use of chemotherapy in early-stage breast cancer.

The baseline MoCA score alone or with age and education predicted the *downward* trajectory better than age or education, and a significant increase in accuracy was obtained when the change in the MoCA score at one year was added to the predictive model, which corresponds to a predictive model with age, education, and the MoCA score at baseline and after one year. Despite the overlap in age, education, MoCA scores and MoCA variation in the first year between the two trajectories, these results show that the five-year trajectory can be accurately predicted considering only variables available within one year of the cancer diagnosis. Similar results were obtained when considering only the one-year MoCA score, which could be of interest in clinical practice. However, cognitive performance one year following the baseline evaluation may have not been the same as if MoCA had been administered for the first time one-year after diagnosis. Indeed, the practice effect needs to be considered in the test result as part of the cognitive performance on a second test.

4.1. Strengths and limitations of our study

Our study is based on the NEON-BC cohort that initially included a large number of women with breast cancer (n = 506) and suffered a low attrition over the five years (7.9%). The complete follow-up consisted of four different moments, including a baseline assessment, after diagnosis and prior to any cancer treatment. This allowed us to describe cognitive trajectories occuring during the continuum of breast cancer care, from diagnosis, to shortly after the completion of treatment, and to long-term care, and to show that some women recover from a pre-treatment cognitive impairment, while others have a declining cognitive trajectory.

We used MoCA to assess cognitive performance overtime, which is one of the most commonly used cognitive screening tests in cancer settings [39] and a comprehensive neuropsychological evaluation may not be available during the clinical care of patients with cancer.

The external validity of our study is limited by the fact that patients with more advanced disease corresponded to a very small part of the cohort and because only one hospital was involved. However, the Portuguese Institute of Oncology of Porto is the largest hospital providing cancer care in Northern Portugal and is the reference hospital of a large geographical area. Additionally, our results can not be generalized to women with breast cancer with

very low cognitive performance at diagnosis, because patients with baseline MoCA scores lower than 17 or 16, if they were older than 65 years, were excluded from the cohort, considering that they were less likely to be able to understand the study and to answer to questionnaires assessing important health outcomes over the five years.

5. Conclusion

This study shows that cognitive decline occurs during the first five years of breast cancer care, with these long-term trajectories being largely influenced by the baseline cognitive performance and its variation in the first year following diagnosis. In this study, the variation in cognitive performance during the first year was essential to more accurately predict worse trajectories, and may allow for the identification of women with a decreased performance who are more likely to develop cognitive decline in the future.

Declaration of competing interest

None declared.

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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.2021.05.006.

Ethical approval

All procedures performed in the present study were approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (ref. CES 406/011, CES 99/014 and CES 290/014) and by the Portuguese Data Protection Authority (ref. 9469/2012 and 8601/2014), and are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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