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Original Research

Mental health outcomes in older breast cancer survivors: Five-year follow-up from the CLIMB study



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Abstract Background: There is a lack of information on mental health outcomes for the increasing older population. Therefore, the aim of the current study is to assess depressive symptoms, loneliness, and apathy in older patients with breast cancer within the first 5 years after diagnosis.

Methods: Women aged ≥ 70 years with early-stage breast cancer were included. Multivariate linear mixed models were used to assess longitudinal changes in symptoms of depression (according to the 15-item Geriatric Depression Scale), loneliness (according to the De Jong

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Gierveld Loneliness Scale) and apathy (according to the Starkstein Apathy Scale) over time at 3, 9, 15, 27 and 60 months follow-up.

Results: In total, 299 patients were included (mean [standard deviation (SD)] age: 75.8 [5.2] years). At 3 months follow-up, shortly after the acute treatment, 10% of patients had significant depressive symptoms, while loneliness and apathy were present in 31% and 41% of all patients, respectively. Depression, loneliness and apathy scores showed no clinically relevant changes over time in the whole cohort. Patients who received adjuvant systemic therapies (i.e. endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) had similar mental health outcomes as those who did not. However, frail patients had more symptoms ($p < 0.001$) and were more prone to develop depressive symptoms over time than non-frail patients ($p = 0.002$).

Discussion: Depression, loneliness and apathy were frequently observed in older women with breast cancer and did not change over time. Patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. However, frail patients were at higher risk to experience these symptoms.

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1. Introduction

Breast cancer is the most frequently diagnosed malignancy in women, and more than 30% of patients are over the age of 70 years at the time of diagnosis [1]. Older patients form a heterogeneous group with disparities in fitness and frailty. Frailty is a condition in which a person's physiological reserve has deteriorated due to the accumulation of ageing processes in multiple organ systems, making them more susceptible to side effects and complications of treatment [2]. Consequently, older patients are often excluded from participating in large randomised controlled trials, making it challenging to guide individualised, evidence-based treatment for older patients. As the proportion of older patients with breast cancer is expected to increase due to ageing populations, more research in this group is needed.

Although prolongation of life has always been the key aim of cancer treatment, a more comprehensive approach is often required, especially in the older population. An important, perhaps sometimes underestimated, aspect of breast cancer care is the impact of breast cancer diagnosis and treatment on mental health and social functioning [3–8]. Mental health is associated with quality of life and may even have implications for treatment adherence and survival [9,10].

Several studies have investigated mental health outcomes in patients with breast cancer [11–14]. However, few studies have focused on older patients and most studies have a short follow-up, while for the majority of patients the processing and acceptance of their diagnosis and disease begins once the acute symptoms of the disease and its treatment have resolved. Therefore, the aim of the current study was to assess depressive symptoms, loneliness and apathy in older women with early-stage breast cancer in the first 5 years after diagnosis.

2. Methods

The Climb Every Mountain study prospectively included women aged 70 years and older with primary, in situ or stage I–III breast cancer from nine Dutch hospitals between 2013 and 2018. Patients were excluded if they had a previous breast cancer history, stage IV disease, were unable to read Dutch, or had advanced dementia. For the current analysis, only patients who completed at least two questionnaires for either depression, loneliness or apathy were included. All patients gave written informed consent, and the study was approved by the medical ethics committee of Leiden University Medical Centre.

2.1. Data collection

Details of this longitudinal cohort study have been extensively described in previous publications [15,16]. In short, a geriatric assessment was performed at baseline, using validated questionnaires on nutritional status (using the Malnutrition Universal Screening Tool (MUST)) [17], cognition (using the Mini-Mental State Examination (MMSE)) [18], functional status (using the Groningen Activity Restriction Scale (GARS)) [19], and mobility (using the Timed Up and Go test (TUG)) [20]. Age, comorbidities (using the Charlson Comorbidity Index, without adjustment for age and breast cancer diagnosis) [21], medication use (categorised as less than five or five or more types of medication), and tumour- and treatment characteristics were also collected at baseline.

Patients were followed up at 3, 9, 15, 27 and 60 months after surgery (Supplemental Fig. 1). Follow-up consisted of multiple assessments and questionnaires, including depression, loneliness and apathy questionnaires. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS) [22,23]. The

15-item GDS is a shortened screening questionnaire to assess depressive symptoms in older adults. The total score ranges from 0 to 15 and a score of 5 or higher indicates clinically relevant depressive symptoms [23]. De Jong Gierveld Loneliness Scale was used to assess loneliness [24,25]. The 11 items add up to a score between 0 and 11 with a cut-off of 3 for moderate loneliness and a cut-off of 9 for severe loneliness [26]. Apathy was evaluated with the Starkstein Apathy Scale [27]. This questionnaire consists of 14 questions with a maximum score of 42. A score of at least 14 is considered indicative for the presence of clinically relevant apathy [28]. If 10% was missing in any of these three questionnaires, the average of the other questions was taken. If more than 10% of a single questionnaire was missing, that questionnaire was scored as 'unknown'. Recurrences were assessed until 27 months after treatment initiation.

Frailty was defined as impairments in two or more domains: cognitive (MMSE < 24), physical (timed up and go > 12 s), somatic (Charlson Comorbidity Index \geq 2 or polypharmacy) or nutrition (high risk on the Malnutrition Universal Screening Tool). Patients with a GARS score of \geq 29 were also considered frail [29].

2.2. Statistical analysis

The chi-square test was used to assess differences between patients who had completed questionnaires on at least two time points and those who had not. Least square means were estimated to evaluate average longitudinal trajectories in depressive symptoms, loneliness and apathy during the first 5 years after diagnosis, using linear mixed models. All three outcome measures were separately analysed as dependent variable, with a random intercept and time as a fixed parameter. To adjust for predefined confounders, baseline characteristics age, tumour stage, Charlson Comorbidity Index, type of surgery, and adjuvant systemic therapy were added as fixed parameters to the models [30,31]. Longitudinal trajectories were evaluated for minimal clinically important changes. According to previous studies, any change of two points on the 15-item GDS questionnaire represents a clinically relevant change [32]. As no thresholds exist for the loneliness and apathy questionnaires, clinical relevance was assessed according to Norman's rule-of-thumb [33]. Norman and his colleagues determined that changes of at least half the standard deviation of the baseline mean are considered clinically relevant.

Second, additional analyses were conducted to assess whether the use of adjuvant systemic therapy (yes or no endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) affected the longitudinal behaviour of depressive symptoms, loneliness and apathy using linear mixed models. An interaction term between

time and adjuvant systemic therapy was added to the model to analyse whether longitudinal changes in depressive symptoms, loneliness and apathy differed between patients who were treated with adjuvant systemic therapy and those who were not. This model was repeated with adjustment for age, tumour stage, Charlson Comorbidity Index, and type of surgery. Of note, the median time between start of endocrine therapy and return of the first questionnaire was 2.5 months (interquartile range (IQR): 1–3 months).

Third, differences in outcomes between frail and non-frail patients were studied using linear mixed models. Interaction terms between time and frailty were used to estimate the difference in longitudinal change between frail and non-frail patients. This model was additionally adjusted for age, tumour stage, Charlson Comorbidity Index, type of surgery, and adjuvant systemic therapy.

Fourth, previous studies showed that patients with vascular diseases are at higher risk of developing apathy [34,35]. Therefore, a sensitivity analysis was performed to assess whether the presence of vascular diseases (i.e. myocardial infarction, angina pectoris, myocardial ischaemia, intermittent claudication, arterial surgery, or stroke) was associated with a higher risk of apathy, using linear mixed models.

The results of all linear mixed models were presented as beta coefficients (β), 95% confidence intervals (CI) and *p*-values. The threshold for a two-sided, statistically significant *p*-value was 0.050. All analyses were performed in SPSS® version 25.0 (IBM, Armonk, New York, USA).

3. Results

A total of 299 patients completed questionnaires on at least two different time points and were included in the current analysis (Supplemental Fig. 1). Compared to patients who were excluded, included patients were younger, had less comorbidities and polypharmacy, were less dependent, had more breast (conserving) surgery, and received more radiotherapy (Supplemental Table 1). In the current analysis, half of all patients were 75 years and older and 123 patients (41.1%) had a Charlson Comorbidity Index of 1 or more (Table 1). Very few patients (2.0%) had cognitive deficits (i.e. MMSE < 24) at baseline. Hundred fifty-eight patients (52.9%) were not completely independent in their activities of daily living and instrumental activities of daily living (i.e. GARS \geq 19). Approximately half of all patients (50.8%) had stage I breast cancer and 246 (82.3%) had oestrogen receptor (ER)-positive tumours. Almost all patients underwent breast surgery (96.3%), of whom 170 patients (56.8%) had breast-conserving surgery and 118 patients (39.5%) a mastectomy. The majority underwent a sentinel lymph node procedure (74.6%). Over half of all patients (51.2%) were not treated with any form of adjuvant systemic treatment, whereas 127

Table 1
Patients-, tumour-, and treatment characteristics at baseline

Age	
70–74	154 (51.5)
75–79	67 (22.4)
80–84	54 (18.1)
≥85	24 (8.0)
TNM stage	
0	11 (3.7)
I	152 (50.8)
II	100 (33.5)
III	18 (6.0)
Unknown	18 (6.0)
Grade	
I	70 (23.4)
II	122 (40.8)
III	91 (30.4)
Unknown	16 (5.4)
ER-status	
Negative	33 (11.0)
Positive	246 (82.3)
Unknown	20 (6.7)
PR-status	
Negative	86 (28.8)
Positive	191 (63.9)
Unknown	22 (7.3)
HER2-status	
Negative	217 (72.6)
Positive	27 (9.0)
Unknown	55 (18.4)
Charlson Comorbidity Index (CCI)	
0	176 (58.9)
1	67 (22.4)
≥2	56 (18.7)
Polypharmacy	
No	177 (59.2)
Yes	108 (36.1)
Unknown	14 (4.7)
BMI	
< 20	12 (4.0)
20–25	102 (34.2)
25–30	116 (38.8)
> 30	68 (22.7)
Unknown	1 (0.3)
Mental status (MMSE)	
Normal (≥24)	276 (92.3)
Impaired (< 24)	6 (2.0)
Unknown	17 (5.7)
Functional status (GARS)	
No dependency (< 19)	138 (46.2)
Some dependency (19–28)	133 (44.5)
Disabled (≥ 29)	25 (8.4)
Unknown	3 (0.9)
Highest education level	
Low	185 (61.9)
Middle	39 (13.0)
High	52 (17.4)
Unknown	23 (7.7)
Employment status during working life	
Full time	70 (23.4)
Part time	84 (28.1)
Housewife	104 (34.8)
Other/Unknown	41 (13.7)
Marital status	
Married/living with partner	143 (47.8)
Divorced/widowed	113 (37.8)

Table 1 (continued)

Never married	13 (4.3)
Unknown	30 (10.0)
Living situation	
Independent	293 (98.0)
Assisted living	5 (1.7)
Unknown	1 (0.3)
Neo-adjuvant systemic treatment	
None	257 (85.9)
Chemotherapy (CT)	5 (1.7)
Endocrine therapy (ET)	19 (6.4)
Unknown	18 (6.0)
Most extensive breast surgery	
No surgery	11 (3.7)
Breast conserving	170 (56.8)
Mastectomy	118 (39.5)
Most extensive axillary surgery	
No axillary surgery	21 (7.0)
Sentinel lymph node procedure	223 (74.6)
Axillary lymph node dissection	52 (17.4)
Unknown	3 (1.0)
Adjuvant systemic treatment	
None	153 (51.2)
Chemotherapy (CT)	10 (3.3)
Endocrine therapy (ET)	127 (42.5)
Combination of ET and CT	9 (3.0)
Adjuvant radiotherapy	
No	116 (38.8)
Yes	183 (61.2)
Adjuvant Herceptin (trastuzumab)	
No	288 (96.3)
Yes	11 (3.7)

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CCI, Charlson Comorbidity Index; BMI, body mass index; MMSE, mini-mental state examination; GARS, Groningen Activity Restriction Scale; CT, chemotherapy; ET, endocrine therapy; TNM, primary tumour, lymph node and metastasis, according to the eighth edition of TNM criteria from the cancer staging manual of the American Joint Committee on Cancer.

patients (42.5%) received endocrine therapy, 10 patients (3.3%) chemotherapy and 9 patients (3.0%) both. Of note, 10 out of 299 (3.3%) patients had a recurrence within 27 months after treatment initiation. Six of them continued to complete questionnaires afterwards, three died soon after and one was lost to follow-up.

3.1. Depression

Thirty-one patients (10.4%) had depressive symptoms three months after diagnosis. After adjustment for pre-defined confounders, depressive scores barely increased over time ($\beta = 0.01$; 95% CI = 0.01–0.02; $p < 0.001$) (Fig. 1). Patients who received adjuvant systemic therapies had similar rates of depression as those who did not ($\beta = -0.02$; 95% CI = -0.61 to 0.57; $p = 0.95$) and the longitudinal trajectories of depressive symptoms were also equal for both groups ($p = 0.73$) (Fig. 2).

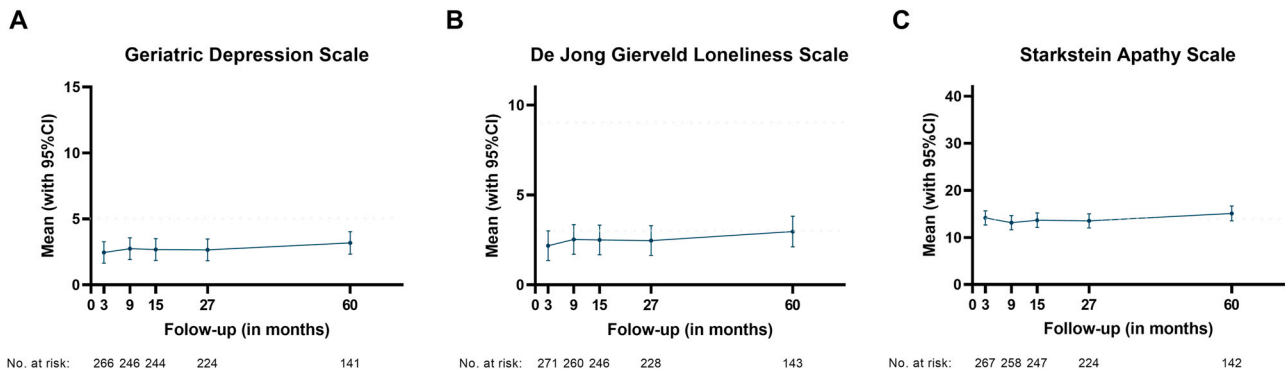


Fig. 1. Depressive symptoms (A), loneliness (B) and apathy (C) over a 5-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

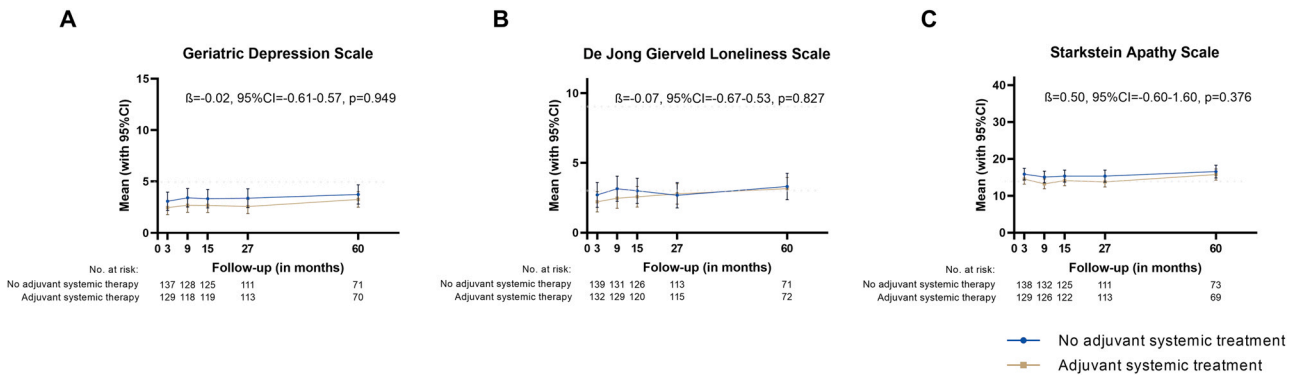


Fig. 2. Depressive symptoms (A), loneliness (B) and apathy (C) stratified for adjuvant systemic therapy over a five-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, and type of breast surgery. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires is described below the graphs.

Patients who were classified as frail at baseline experienced more depressive symptoms over the entire study period than non-frail patients ($\beta = 2.13$; 95% CI = 1.25–3.01; $p < 0.001$) (Fig. 3). Moreover,

according to the statistically significant interaction term between frailty and time ($p = 0.002$), frail patients developed (clinically significantly) more depressive symptoms during follow-up than non-frail patients.

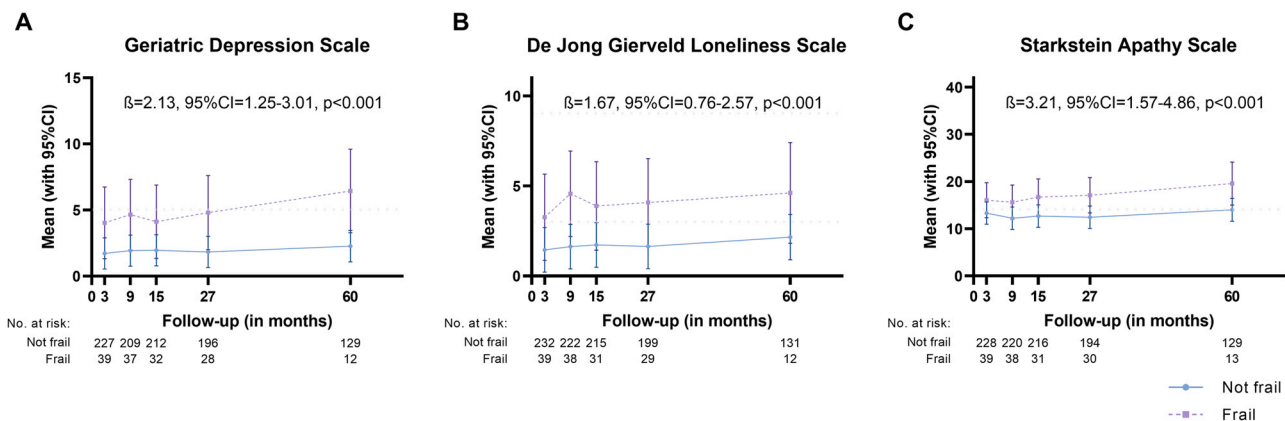


Fig. 3. Depressive symptoms (A), loneliness (B) and apathy (C) stratified for frailty over a five-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

3.2. Loneliness

Ninety-two patients (30.8%) experienced loneliness at three months follow-up, of whom 83 (27.8%) had moderate and 9 (3.0%) severe loneliness. Linear mixed models showed a very small increase in symptoms over time ($\beta = 0.01$; 95% CI = 0.01–0.02; $p < 0.001$) (Fig. 1). Patients treated with adjuvant systemic therapy were not lonelier than patients not treated with adjuvant systemic therapy ($\beta = -0.07$; 95% CI = -0.67 to 0.53; $p = 0.83$) and their longitudinal trajectories were similar ($p = 0.05$) (Fig. 2). Patients who were classified as frail at baseline were lonelier than non-frail patients ($\beta = 1.67$; 95% CI = 0.76–2.57; $p < 0.001$). Moreover, frail patients had mean scores above the clinically relevant threshold for moderate loneliness over the entire study period, while non-frail patients did not (Fig. 3). The longitudinal changes were the same for frail and non-frail patients ($p = 0.52$).

3.3. Apathy

Apathy was prevalent in 121 patients (40.5%) at 3 months after diagnosis and the average apathy score grew marginally each month ($\beta = 0.02$; 95% CI = 0.01–0.04; $p = 0.002$) (Fig. 1). Patients who were treated with adjuvant systemic therapy had similar apathy scores ($\beta = 0.50$; 95% CI = -0.60 to 1.60; $p = 0.38$) and similar longitudinal trajectories over time ($p = 0.31$) than patients without adjuvant systemic therapy (Fig. 2). Frail patients scored worse on the apathy questionnaire than non-frail patients during follow-up ($\beta = 3.21$; 95% CI = 1.57–4.86; $p < 0.001$), exceeding the threshold for clinically relevant apathy (Fig. 3). Moreover, frail patients developed more apathy during follow-up than non-frail patients ($p = 0.03$). Vascular diseases at baseline were not associated with a higher occurrence of apathy over the entire study period ($\beta = 0.26$; 95% CI = -1.44 to 1.95; $p = 0.77$) and were not associated with an increased risk of developing apathy over time ($p = 0.69$).

4. Discussion

This real-world multicentre cohort study of older women with early-stage breast cancer showed that shortly after surgery, 10%, 31% and 41% of patients had depressive symptoms, loneliness and apathy, respectively. Longitudinal trajectories of these outcomes did not change clinically significantly in the first 5 years of follow-up for the whole group. Importantly, patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. Frail patients had more symptoms after surgery and were more prone to developing clinically relevant depression over time.

A recent systematic review showed that single (divorced or widowed) women who have a low income, an advanced diagnosis, functional limitations, comorbidities, and low social support are at higher risk of emotional distress, which are all factors inherent in many older patients with breast cancer [30]. Our study showed that around a third of older patients experienced loneliness after the acute phase of treatment and that frail patients were more likely to be lonely than non-frail patients. The prevalence of loneliness is consistent with previous reports. Deckx and colleagues found that 22% of around one hundred older patients with early-stage breast or colorectal cancer were lonely at the time of diagnosis and 35% at 1-year follow-up [6]. De Boer et al. demonstrated that one-third of older patients with metastasised breast cancer ($N = 80$) experienced loneliness at baseline and throughout a 6-month follow-up period [36]. To put the high prevalence of loneliness among breast cancer survivors into perspective, a previous study found that 39% of older adults from the general population without cancer experienced loneliness [6]. Nevertheless, extensive research has shown that loneliness is a major health concern as it is associated with unhealthy behaviours, impaired physical functioning, worse quality of life, and increased morbidity and mortality [37,38]. Therefore, this high prevalence still requires further attention. Effective loneliness interventions already exist, but sample sizes are small and no studies have specifically focused on older patients with breast cancer [39–42].

Depression is generally quite common in breast cancer survivors, with a prevalence ranging from 8% to 66% [12,13,43,44]. The occurrence of clinically relevant depression in the current study is similar to what has been previously reported in the general older population (5–15%) and much lower than has been found in the advanced setting (46%) [36,43,45]. This relatively low percentage of depressive symptoms in older breast cancer survivors may reflect different treatment allocation and an increased psychological resilience in this age group due to their life stage, while the latter is probably less in frail older patients. Moreover, the majority of patients in the current analysis had hormone receptor-positive disease in which recurrences rarely occur within the first 5 years. According to a study at longer follow-up (cross sectional at 5–16 years post-diagnosis), older breast cancer survivors without recurrences had similar depression rates as controls with no history of breast cancer [46]. However, patients aged 80 years and younger with a recurrence had considerably higher rates of depression than their controls, but not when they were 80–89 years old.

A less frequently reported mental health outcome in patients with breast cancer is apathy [47]. Apathy is characterised by diminished goal-directed behaviour, cognition and emotion, leading to reduced daily functioning [48]. Apathy can be present as a symptom of

depression, but can also occur on its own [49]. A previous study of over 1100 Dutch community-dwelling older adults aged 75 years and older found that 11% of them experienced apathy [28]. This percentage is much lower than was found in our study of older patients with breast cancer and than what has been previously reported in the advanced setting [36]. Apathy is often overlooked by physicians as it is usually not perceived as a nuisance by patients themselves. Moreover, patients with apathy typically have low degrees of suffering and tend to be indifferent, which can result in neglect and caregiver distress [50]. As apathy also interferes with poor treatment adherence and outcome, it requires further attention [51]. There are currently no specific interventions available for this population.

Although it is difficult to identify an aetiological association between systemic therapy and mental health outcomes, endocrine therapy and chemotherapy are believed to exacerbate it, especially depressive symptoms. Fear of these side effects may be a reason for withholding therapy. Nevertheless, the current study showed no difference in apathy, loneliness and depression in patients treated with adjuvant systemic therapy and those not. The results suggest that adjuvant systemic therapy in older patients should not be withheld in fear of worse mental health outcomes, although it must be noted that in this observational cohort, patients with pre-existing mental health problems may have been more reluctant to start adjuvant treatment.

Previous research has shown that patients are reluctant to ask for psychological help [52]. Also, healthcare professionals are not always familiar with all psychological care facilities, do not know how to discuss these topics or simply lack time to do so [52]. Nevertheless, it is important for patients, caregivers and physicians to be aware of the potential impact of cancer and its treatment on mental health outcomes, as well as the possibility of psychosocial support. Psychological care should therefore be given more prominence in breast cancer care to ensure timely detection of patients with a wish for referral to psychological care. Training in communication skills for physicians proved useful in integrating the discussion on mental health outcomes into daily clinical practice [53].

The most important strength of this study is its longitudinal design with extensive information on older women with breast cancer. The study also has limitations. Although the intention was to include all women aged 70 years and older with breast cancer into our study, a relatively fit older population was included. Since frailty exacerbates depressive symptoms, loneliness and apathy, the current study may underestimate the prevalence of these outcomes. Nevertheless, the current study revealed that depressive symptoms, loneliness and apathy are common and frailty probably warrants more attention by physicians. Another limitation of the study is that patients that

experienced disease recurrence were not excluded from follow-up, which may have impacted the outcome. However, the number of recurrences was very small, so the impact of this factor is likely to be limited. Furthermore, the first questionnaires on depression, loneliness and apathy were completed at a median time of three months after surgery (IQR: 3–4 months). It is therefore difficult to draw conclusions about the direct effect of surgery on these mental health outcomes. However, baseline questionnaires on mental health outcomes may be burdensome for patients at the time of diagnosis (as the questionnaires are quite time-consuming) and the results at that time may also be biased because of the large mental stress the cancer diagnosis already brings.

In conclusion, depression, loneliness and apathy are common in older women with breast cancer, especially in frail patients. Although depressive symptoms and loneliness do not appear to be more prevalent than in the general older population, apathy is. Importantly, adjuvant systemic therapy does not seem to exacerbate these symptoms. As mental health outcomes may interfere with adherence to therapy, survival and quality of life, it is important to address the potential impact of cancer on mental health outcomes and to inform patients about the possibility of psychosocial support.

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CRediT authorship contribution statement

Conceptualization; GJL, NAdG, JEAP, Data curation; NAdG, MGMD, AAL, Formal analysis; NAdG, EB, AAL, Funding acquisition; GJL, NAdG, JEAP, Investigation; JEAP, GJL, NAdG, AAL, Methodology; JEAP, GJL, NAdG, AAL, MGMD, NRO, Project administration; NAdG, MGMD, AAL, Resources; JEAP, Software; AAL, NAdG, MGMD, Supervision; JEAP, GJL, NAdG, MGMD, NRO, Validation; NAdG, MGMD, Visualization; AAL, Roles/Writing—original draft; AAL, NAdG, MGMD, JEAP, GJL, Writing—review & editing; all authors.

Data availability

The dataset generated during and analysed during the current study are not publicly available due to participant privacy but are available from the corresponding author on reasonable request.

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2023.04.001](https://doi.org/10.1016/j.ejca.2023.04.001).

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