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Predicting postoperative complications and their impact on quality of life and functional status in older patients with breast cancer

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Abstract

Background: The percentage of older patients undergoing surgery for early-stage breast cancer has decreased over the past decade. This study aimed to develop a prediction model for postoperative complications to better inform patients about the benefits and risks of surgery, and to investigate the association between complications and functional status and quality of life (QoL).

Methods: Women aged at least 70 years who underwent surgery for Tis–3 N0 breast cancer were included between 2013 and 2018. The primary outcome was any postoperative complication within 30 days after surgery. Secondary outcomes included functional status and QoL during the first year after surgery, as assessed by the Groningen Activity Restriction Scale and the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BR23 questionnaires. A prediction model was developed using multivariable logistic regression and validated externally using data from the British Bridging the Age Gap Study. Linear mixed models were used to assess QoL and functional status over time.

Results: The development and validation cohorts included 547 and 2727 women respectively. The prediction model consisted of five predictors (age, polypharmacy, BMI, and type of breast and axillary surgery) and performed well in internal (area under curve (AUC) 0.76, 95 per cent c.i. 0.72 to 0.80) and external (AUC 0.70, 0.68 to 0.72) validations. Functional status and QoL were not affected by postoperative complication after adjustment for confounders.

Conclusion: This validated prediction model can be used to counsel older patients with breast cancer about the postoperative phase. Postoperative complications did not affect functional status nor QoL within the first year after surgery even after adjustment for predefined confounders.

Introduction

Older women with breast cancer comprise a heterogeneous group with large differences in fitness and frailty. The relative efficacy and risk of complications from treatment, and impact on longer-term physical function and quality of life (QoL) may therefore vary widely. Consequently, it might not be appropriate to extrapolate the results of clinical trials based on younger and relatively healthy patients to older patients with breast cancer.

As a result, clinicians frequently deviate from standard treatment owing to patients' advanced age, co-morbidities, frailty or patients' preferences^{1–3}, leading to a lower proportion undergoing surgery and a higher proportion treated with primary endocrine therapy than among younger patients^{4–6}. In the Netherlands, the percentage of patients aged 75 years or older

with stage I–II breast cancer who did not undergo surgery increased significantly from 11.8 per cent in 2000 to 32.1 per cent in 2017⁷. It is questionable whether withholding surgery is justified, as postoperative morbidity and mortality rates following breast cancer surgery are low^{8,9}.

Survival is arguably the most important outcome in cancer treatment. It is also important to consider possible complications of treatment and their long-term impact on QoL, which may be relatively more important to older women¹⁰. Varying incidence rates of postoperative complications have been reported, ranging from 2 to 50 per cent^{8,9,11–14}. The most frequently reported complications are wound infections and seroma formation. Although these complications may be considered relatively innocuous, they might have a great impact on the functional

status and QoL of those affected. These aspects have received limited attention but are significant in the breast cancer population^{10,15}. It is therefore important to identify patients at risk of developing postoperative complications, and to assess the impact of these complications on QoL and functional performance.

The objective of this study was to develop and validate a risk prediction model for postoperative complications in older patients with breast cancer using clinical and geriatric predictive factors, and to evaluate whether postoperative complications affect both functional status and QoL in the first year after surgery.

Methods

Design and study population of development cohort

Patients who underwent surgery were selected from the prospective and longitudinal CLIMB (Climb Every Mountain) cohort study. This study included patients aged 70 years and older with primary breast cancer (Tis–3 N0–3) between 2013 and 2018 in nine Dutch hospitals. Exclusion criteria were a previous breast cancer history, distant metastases, inability to read Dutch, and advanced dementia. The study was approved by the medical ethics committee of Leiden University Medical Centre.

Data collection for development cohort

A geriatric assessment was conducted at diagnosis as standard care, which included a history of co-morbidities, use of medication, nutritional status (Malnutrition Universal Screening Tool)¹⁶, cognition (Mini Mental State Examination, MMSE)¹⁷, physical function (Timed Up and Go test)¹⁸, and functional status (Groningen Activity Restriction Scale, GARS)¹⁹. The GARS is a validated questionnaire assessing 11 activities of daily living and seven instrumental activities of daily living. Patients were requested to indicate whether they could perform these activities, with or without assistance. Answers were given on a scale of 1–4, where 1 stands for being able to perform the actions independently and 4 indicates complete dependency. The total score ranges from 18 to 72, with higher scores indicating worse functional status. The GARS was categorized into four groups (below 19, no dependency; 19–28, some dependency; 29 or more, disabled; unknown, data missing)^{20–22}. If less than 10 per cent of the answers were missing (only 1 question), the average mean score for the other answers was taken and recorded. If more than 10 per cent of answers in an independent questionnaire were missing, the score for the whole questionnaire was classified as unknown.

One week after the geriatric assessment, eligible women were asked to confirm whether they wanted to participate in the CLIMB study and written informed consent was obtained from all participants. The CLIMB study comprised three follow-up visits, 3, 6, and 12 months after diagnosis. At each follow-up, clinical data, including patient, tumour, treatment characteristics, and complications were retrieved from the medical records. The follow-up visits also included multiple assessments and completion of questionnaires, including cognition (MMSE), physical function (Timed Up and Go test), functional status (GARS), and QoL (Table S1). QoL was assessed by means of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and its breast cancer-specific module, QLQ-BR23^{23–25}. The optional questions in the breast cancer-specific module concerning sexual function, sexual enjoyment, and upset by hair loss were excluded from the total score, as these questions were answered by only a limited

number of women. For the QLQ-C30 scores, the outcome was assessed as clinically relevant according to the findings of Musoro and colleagues²⁶. For the QLQ-BR23 questionnaire, a difference of 10 points or more was considered clinically relevant²⁷.

To obtain as much information as possible on CLIMB cohort participants, including those not attending follow-up visits, information on tumour characteristics, treatment, and complications were retrieved from the medical records 1 year after diagnosis (Fig. S1).

Design and study population of validation cohort

Patients who underwent surgery were selected from the Bridging the Age Gap in Breast Cancer study. Extensive details of the procedures of this cohort have been published elsewhere^{14,28}. In short, this was a prospective, multicentre, observational cohort study of women aged 70 years or older with primary operable invasive breast cancer, diagnosed between 2013 and 2018 at 56 breast units in England and Wales. Similar data items were recorded, including QLQ-C30 scores (Table S1). The Age Gap cohort recruited women with dementia, but these were excluded from the present analyses to give a more comparable data set to the CLIMB cohort.

Classification of variables

Patients were assigned to three groups according to age (70–74, 75–79, 80 years or more). Tumour size was classified as 0–2 cm, larger than 2 cm or unknown. If the pathological size was missing, the clinical size was used. Nodal status was classified as either no positive nodes (N0) or at least one positive node (N+). If the pathological lymph node status was not recorded, the clinical stage was used. Breast surgery was categorized as breast-conserving surgery, mastectomy or unknown. If patients initially underwent breast-conserving surgery and a later mastectomy, the most extensive procedure was used in the analyses. Axillary surgery was classified as sentinel node biopsy, axillary lymph node dissection (ALND) or unknown. Patients who underwent sentinel node biopsy first followed by a later completion ALND were classified as having had the latter. Any co-existing diseases were registered according to the Charlson Co-morbidity Index (CCI), without adjustment for age^{29–31}. Breast cancer was not included, because this index quantifies the presence of co-existing diseases at breast cancer diagnosis. BMI was subdivided into four groups (less than 20.0, 20.0–24.9, 25.0 kg/m² or more, unknown). Polypharmacy was defined as taking five or more types of medication, and documented as yes, no or unknown³².

Outcome

The primary outcome was any postoperative complication, defined as any complication occurring within 30 days after surgery requiring treatment measures not applied routinely after surgery. Secondary outcomes were QoL and functional status after 3, 6, and 12 months in patients with and without postoperative complications.

Statistical analysis

The χ^2 test and Fisher's exact test were used to assess differences between patients who participated in the CLIMB and Age Gap cohorts. Predetermined potential risk factors were examined in univariable logistic regression analyses to calculate odds ratios (ORs) with 95 per cent confidence intervals and P values for the association between risk factors as independent variables and

postoperative complications as the dependent variable. These predictors for the univariable model were based on earlier research, and consisted of age, nodal status, tumour size, type of (axillary) surgery, CCI score, BMI, polypharmacy, Malnutrition Universal Screening Tool score, the Timed Up and Go test, and functional status (GARS)^{11–13,33–38}. A prediction model was built by using multivariable logistic regression analysis that included the statistically significant outcomes of the univariable logistic regression analyses, in combination with variables identified in previous studies. A receiver operating characteristic (ROC) curve was used to test internal validity of the prediction model, by calculating the area under the curve (AUC). After selecting the model with the highest AUC, points were attributed to each predictor by creating a Kattan-style nomogram³⁹. For internal validation, bootstrapping was performed 1000 times to avoid overfitting of the model. External validation was also undertaken with construction of a ROC curve and calibration plots. Calibration was performed by creating three equally large groups, consisting of patients with a low, medium or high probability of developing a postoperative complication.

Functional status and QoL were assessed by plotting graphs of mean scores at each time point with corresponding standard deviations (SD) for patients with and without postoperative complications. Multivariable linear mixed models were used to assess whether this changed significantly over time. An advantage of linear mixed models is that they also include incomplete patient sets, by assuming that the data are missing at random⁴⁰. Functional status and QoL were both analysed separately as dependent variables with postoperative complications as independent categorical variable and time after surgery (3, 6, and 12 months) as independent continuous variable. All predefined confounders were added to the model as fixed variables. These predefined confounders were age, nodal status, tumour size, polypharmacy, co-morbidities, and BMI^{15,41–46}. Any interaction between postoperative complications and time was tested to assess whether complications were time-dependent. For sensitivity analysis, QoL and functional status were analysed with inclusion of only seromas as postoperative complication.

All analyses were performed in SPSS® version 25.0 (IBM, Armonk, New York, USA) and Stata® SE version 16.0 (StataCorp, College Station, Texas, USA). For all analyses, the threshold for a two-sided, statistically significant P value was 0.050.

Results

The present study included a total of 547 women from the CLIMB cohort and 2727 women from the Age Gap cohort with breast cancer (Tis–3 N0–3), who underwent surgery and for whom outcome data were available (Fig. S1). Patient and tumour characteristics of the development (CLIMB) and validation (Age Gap) cohorts are shown in Table 1. Almost three-quarters of the patients ranged in age from 70 to 79 years (71.3 and 73.6 per cent in CLIMB and Age Gap cohorts respectively). The majority of patients had lymph node-negative disease (79.7 and 84.3 per cent). Most patients underwent breast-conserving therapy (56.1 and 60.5 per cent), and had a sentinel node procedure (74.6 and 78.2 per cent). Almost half of all patients had a CCI score of 1 or higher (46.4 and 48.3 per cent).

Postoperative complications

A total of 285 complications occurred in 224 patients (41.0 per cent) in the CLIMB population, and 1205 complications in 984 patients

(36.1 per cent) in the Age Gap cohort (Table 2). Some patients had more than one complication (57 and 190 patients respectively). The most frequent complications were seromas (26.3 per cent in both cohorts), wound infections (9.5 and 5.8 per cent), and haematomas (9.0 and 6.2 per cent). In the CLIMB cohort, two

Table 1 Patient characteristics in the two cohorts

	CLIMB	Age Gap	P*
Age (years)			<0.001
70–74	270 (49.4)	1145 (42.0)	
75–79	120 (21.9)	863 (31.6)	
≥ 80	157 (28.7)	719 (26.4)	
Nodal status			<0.001
N0	436 (79.7)	2298 (84.3)	
N+	88 (16.1)	428 (15.7)	
Unknown	23 (4.2)	1 (0.0)	
Tumour size (cm)			<0.001
0–2	348 (63.6)	1650 (60.5)	
> 2	193 (35.3)	1077 (39.5)	
Unknown	6 (1.1)	0 (0)	
Breast surgery			0.059
Breast-conserving	307 (56.1)	1649 (60.5)	
Mastectomy	240 (43.9)	1078 (39.5)	
Axillary surgery			<0.001
None	34 (6.2)	85 (3.2)	
Sentinel node biopsy	408 (74.6)	2133 (78.2)	
Axillary lymph node dissection	99 (18.1)	508 (18.6)	
Unknown	6 (1.1)	1 (0.0)	
Charlson Comorbidity Index score			<0.001
0	293 (53.6)	1411 (51.7)	
1	133 (24.3)	452 (16.6)	
≥ 2	121 (22.1)	864 (31.7)	
BMI (kg/m²)			<0.001
20.0–24.9	173 (31.6)	676 (24.8)	
≥ 25.0	352 (64.4)	1557 (57.1)	
< 20.0	20 (3.6)	88 (3.2)	
Unknown	2 (0.4)	406 (14.9)	
Polypharmacy			<0.001
No	305 (55.8)	1571 (57.6)	
Yes	219 (40.0)	1156 (42.4)	
Unknown	23 (4.2)	0 (0)	
Functional status (GARS score)			
< 19	230 (42.0)		
19–28	234 (42.8)		
≥ 29	73 (13.4)		
Unknown	10 (1.8)		

Values in parentheses are percentages. GARS, Groningen Activity Restriction Scale. * χ^2 or Fisher's exact test.

Table 2 Postoperative complications that required treatment in first 30 days in both cohorts

	CLIMB	Age Gap	P*
All complications	285 (52.1)	1205 (44.2)	0.001
Patients with at least one complication	224 (41.0)	984 (36.1)	0.031
Wound infection	52 (9.5)	158 (5.8)	0.002
Haemorrhage	17 (3.1)	28 (1.0)	0.001
Seroma	144 (26.3)	718 (26.3)	0.983
Haematoma	49 (9.0)	169 (6.2)	0.018
Lymphoedema	14 (2.6)	13 (0.5)	<0.001
Death	2 (0.4)	0 (0)	0.074
Necrosis	0 (0)	17 (0.6)	0.095
Wound, non-infectious	5 (0.9)	42 (1.5)	0.263
Somnolence	0 (0)	32 (1.2)	0.007
Allergic reaction	0 (0)	4 (0.1)	1.000
Arrhythmia	0 (0)	12 (0.4)	0.237
Embolism, infarction, stroke	2 (0.4)	10 (0.4)	1.000
Atelectasis	0 (0)	1 (0.0)	1.000

Values in parentheses are percentages. * χ^2 or Fisher's exact test.

patients (0.4 per cent) died within 1 week after surgery, whereas no patient in the Age Gap cohort died within 30 days after surgery.

Age, nodal status, tumour size, type of breast surgery, type of axillary surgery, and the Timed Up and Go test were statistically significantly associated with postoperative complications in a univariable logistic regression model (Table S2). In the multivariable logistic regression model, the effect of nodal status, tumour size, and the Timed Up and Go test disappeared, and so these variables were omitted from the final model. The final model included five predictors: polypharmacy, BMI, type of axillary surgery, type of breast surgery, and age. In the final model, the type of breast surgery was strongly correlated with postoperative complications. Mastectomies had higher rates of postoperative complications than breast-conserving surgery (OR 5.27, 95 per cent c.i. 3.50 to 7.93; $P < 0.001$) (Table 3 and Fig. S2). Patients aged 80 years or more had significantly higher rates of complications than those aged between 70 and 74 years (OR 1.70, 1.06 to 2.72; $P = 0.029$).

Validation

The AUC for the development cohort was 0.76 (95 per cent c.i. 0.72 to 0.80) after bootstrapping, compared with 0.70 (0.68 to 0.72) for the external validation cohort. In both cohorts, the risk of postoperative complications increased with increasing risk score (14.8 versus 20.4 per cent in low-risk group, 43.3 versus 32.7 per cent in medium-risk group, and 67.2 versus 56.4 per cent in high-risk group in development and validation cohorts respectively; $P < 0.001$) (Fig. 1).

Functional status and quality of life

For analyses of QoL and functional status, only participants who were enrolled for the follow-up questionnaires and who did not withdraw consent before the first follow-up (320 patients) were included from the CLIMB cohort. The response rate was 92.8 per cent (297 of 320 patients) after 3 months, 85.6 per cent (255 of 298) after 6 months, and 89.5 per cent (248 of 277) after 12 months (Fig. S1).

Table 3 Multivariable logistic regression analysis of association between patient characteristics and occurrence of postoperative complications in the CLIMB and Age Gap cohorts

	CLIMB			Age Gap		
	No. of patients	Odds ratio*	P	No. of patients	Odds ratio*	P
Age (years)			0.086			0.313
70–74	270 (49.4)	1.00 (reference)		1145 (42.0)	1.00 (reference)	
75–79	120 (21.9)	1.13 (0.68, 1.89)		863 (31.6)	0.92 (0.75, 1.12)	
≥ 80	157 (28.7)	1.70 (1.06, 2.72)		719 (26.4)	1.08 (0.88, 1.34)	
Breast surgery			<0.001			<0.001
Breast-conserving	307 (56.1)	1.00 (reference)		1649 (60.5)	1.00 (reference)	
Mastectomy	240 (43.9)	5.27 (3.50, 7.93)		1078 (39.5)	3.35 (2.81, 4.00)	
Most extensive axillary surgery			<0.001			<0.001
No axillary surgery	34 (6.2)	1.00 (reference)		85 (3.2)	1.00 (reference)	
Sentinel node procedure	408 (74.6)	0.48 (0.22, 1.05)		2133 (78.2)	1.23 (0.75, 1.99)	
Axillary lymph node dissection	99 (18.1)	2.20 (0.91, 5.32)		508 (18.6)	2.29 (1.37, 3.81)	
Unknown	6 (1.1)	1.51 (0.23, 10.12)		1 (0.0)	–†	
BMI (kg/m²)			0.766			0.924
20.0–24.9	173 (31.6)	1.00 (reference)		676 (24.8)	1.00 (reference)	
≥ 25.0	352 (64.4)	1.25 (0.81, 1.92)		1557 (57.1)	0.95 (0.77, 1.16)	
< 20.0	20 (3.6)	0.96 (0.33, 2.81)		88 (3.2)	0.88 (0.54, 1.44)	
Unknown	2 (0.4)	–†		406 (14.9)	0.93 (0.69, 1.25)	
Polypharmacy			0.613			0.183
No	305 (55.8)	1.00 (reference)		1571 (57.6)	1.00 (reference)	
Yes	219 (40.0)	1.17 (0.77, 1.76)		1156 (42.4)	1.13 (0.95, 1.35)	
Unknown	23 (4.2)	0.74 (0.25, 2.19)		0 (0)	–†	

Values in parentheses are percentages unless indicated otherwise; *value in parentheses are 95 per cent confidence intervals. †Could not be calculated because of the small numbers.

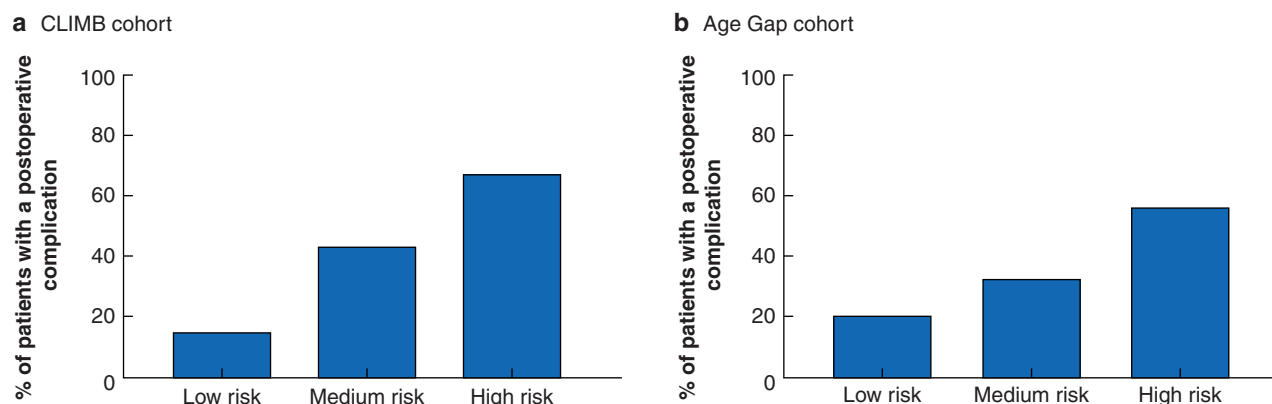


Fig. 1 Calibration of prediction tool in the development (CLIMB) and validation (Age Gap) cohorts

a CLIMB cohort and b Age Gap cohort. a,b $P < 0.001$ (chi-square test).

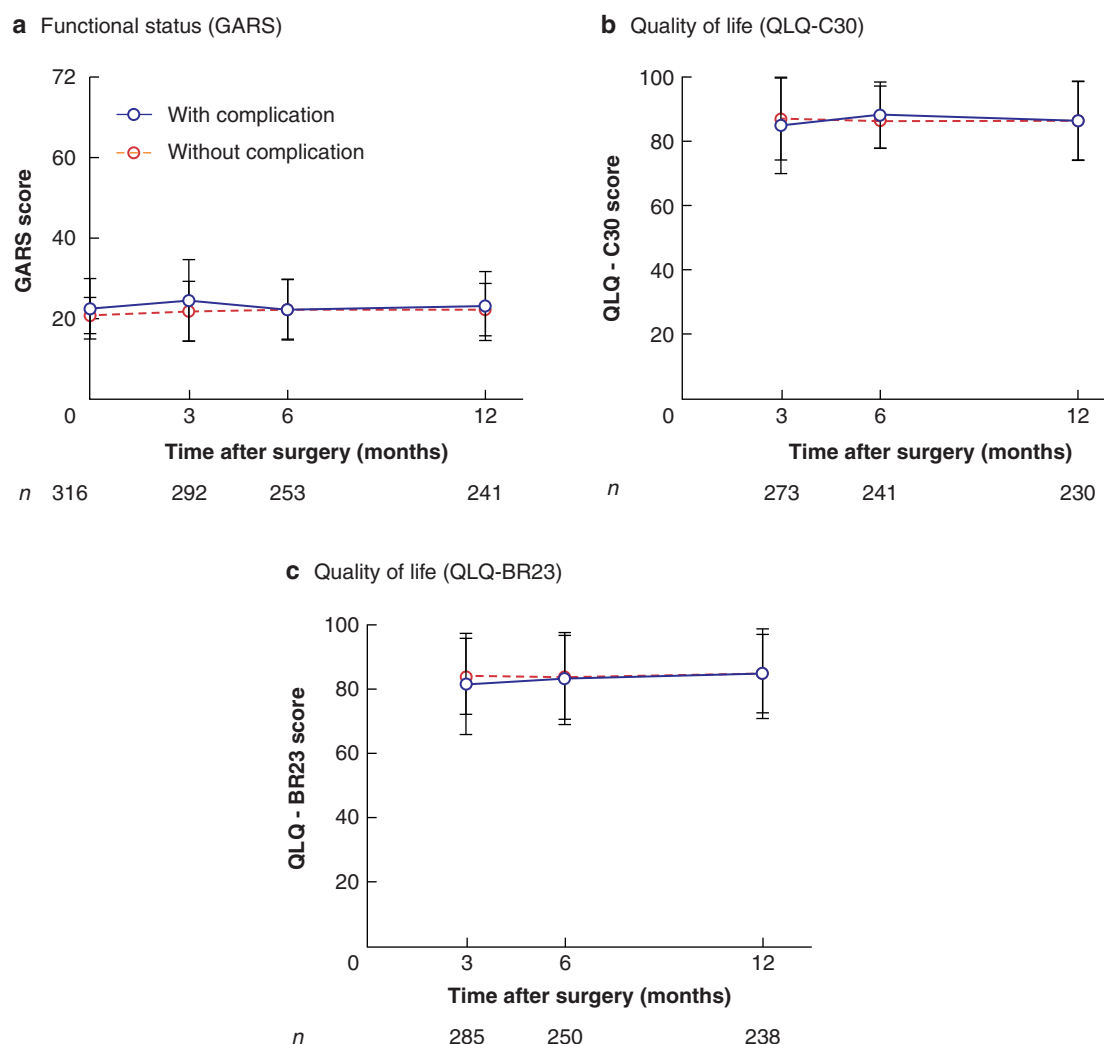


Fig. 2 Functional status and quality of life over time in CLIMB cohort

a Functional status (Groningen Activity Restriction Scale, GARS), **b**, quality of life assessed using the EORTC QLQ-C30 and **c** its breast-specific module QLQ-BR23. A higher GARS score denotes a worse functional status, whereas a higher QLQ score indicates better quality of life. Values are mean(s.d.).

Patients with postoperative complications had statistically significantly higher mean GARS scores than those without any complication, indicating worse functional status ($b = 1.96$, 95 per cent c.i. 0.64 to 3.28; $P = 0.004$) (Table S3 and Fig. 2a). This effect was, however, very small and no longer significant when adjusted for predefined confounders ($b = 0.51$, -0.68 to 1.71 ; $P = 0.402$). No statistically significant interaction was found between time and postoperative complications with regard to functional status ($b = -0.11$, -0.32 to 0.10 ; $P = 0.291$), indicating that changes in functional status did not differ over time between patients with or without a postoperative complication. The association between postoperative complications and effect on functional status was also analysed separately for seromas. Again, no statistically significant or clinically relevant difference was found in functional status after adjustment for predefined confounders (results not shown).

There was no statistically significant difference in QoL between patients with or without postoperative complications in either the generic ($b = -1.43$, -5.19 to 2.32 ; $P = 0.453$) or breast cancer-specific questionnaire ($b = -2.59$, -6.56 to 1.38 ; $P = 0.200$) (Table S3 and Fig. 2b,c). Body image scores were significantly lower among patients with a postoperative complication after correction for predefined confounders ($b = -4.98$, -9.07 to -0.89 ; $P = 0.017$). This impact on

body image was probably explained by the type of surgery performed, as the effect disappeared when corrected for type of surgery. Moreover, a difference of 4.98 points on the body image scale is small and therefore not clinically relevant²⁷. None of the other subscale scores showed any statistically significant differences. Seromas did not affect QoL in the first year after surgery (results not shown).

Discussion

In the present study, 41.0 per cent of older patients with breast cancer developed a postoperative complication within 30 days after surgery. A prediction tool was designed for complication risk, with good internal and external validity. Postoperative complications did not affect functional status or QoL in the first year after surgery after adjustment for predefined confounders.

The number of older patients with breast cancer who undergo surgery varies widely between European countries⁴⁷. A recent study⁷ showed that the number of patients with stage I-II breast cancer aged over 75 years receiving surgery decreased, and the percentage of those who received endocrine therapy (either neoadjuvant or adjuvant or as primary treatment) increased, between 2000 and 2017. Moreover, breast cancer-specific and

overall survival is worse for patients receiving primary endocrine therapy compared with those undergoing surgery followed by adjuvant endocrine therapy^{28,48}. The reason for this recent change in treatment strategy is unknown, but might be based on fear of postoperative complications, and loss of independence and QoL⁴⁹. The probable survival benefit for operated patients, combined with the present findings that postoperative complications do not affect QoL or functional status in the first year after diagnosis, might not justify this decrease in patients receiving surgical treatment.

The present results have shown that postoperative complications do not have a clinically relevant impact on QoL and functional status over time. In contrast, a previous study⁴³ of nearly 6000 nursing home residents in the USA noted a functional decline in 58 per cent of women 1 year after breast cancer surgery. One could argue, however, that nursing home residents may naturally exhibit a decline in functional status, regardless of interventions, and were probably older and more frail than the average patient in the CLIMB and Age Gap cohorts⁵⁰. Earlier research from Wyld and co-workers²⁸, using data from over 2000 UK women aged over 70 years in the Age Gap study, found that breast cancer surgery was associated with a small functional decline in the first 6 weeks after surgery, which did not recover even after 2 years. This difference might, however, be explained by the fact that only one question was asked concerning ability to perform usual activities, whereas the present study used a complete questionnaire (GARS) designed to measure functional status. Regarding QoL, the same study showed a decline in mean global health status between baseline and 6 weeks after surgery that did not recover within 24 months²⁸. Musoro *et al.*²⁶ however, have questioned the clinical significance of this finding. In another study⁵¹ of more than 6000 women who underwent mastectomy, one-third above 65 years of age, a statistically significant difference was found between women with and without complications in terms of physical well-being, emotional well-being, and breast area appearance score. These differences were, however, mostly considered clinically insignificant.

The high incidence of postoperative complications in the present study concurs with earlier reports^{8,11–13}. Results from the Age Gap study¹⁴ showed that only 19 per cent of operations resulted in a postoperative complication. However, in contrast to the present study, seromas were not taken into account. Consistent with previous studies^{8,11,13}, type of surgery was found to be a predictor of development of postoperative complications. Several studies^{8,11–13,35,36} have investigated the effect of age, co-morbidities, polypharmacy, BMI or functional status on complication rates, but the results are very inconsistent. No statistically significant association between these factors and the incidence of postoperative complications was found here, possibly because of a smaller sample size.

As for many other decisions in medicine, it is important to inform every patient about possible treatment outcomes to improve the shared decision-making process. Previous research^{49,52} has shown that surgeons seem to underestimate patients' desire for information about the risk of complications. The prediction tool presented could therefore be used to calculate the individual risk of postoperative complications after breast cancer surgery to create awareness of possible consequences, such as more hospital visits and additional treatment measures.

The strengths of this study include its prospective design with highly detailed information regarding older patients with breast

cancer at baseline and during follow-up, with a high response rates (85.6–92.8 per cent). The study also has limitations. The aim was to target all women aged 70 years and older with breast cancer, but patients who discontinued from the study had more polypharmacy, and worse functional status and physical functioning than those for whom follow-up data were available. This form of selection bias was also observed in the completed questionnaires during follow-up. Furthermore, owing to differences in assessments at baseline and during follow-up, QoL was not assessed at baseline. Therefore, any changes in QoL between baseline and postoperative time points could not be determined. It is therefore difficult to draw conclusions about complications and QoL. To further improve treatment strategies for older patients with breast cancer, future research should focus more on QoL and functional status, after both primary endocrine therapy and surgery.

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Supplementary material

Supplementary material is available at BJS online.

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