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Article

Long-term behavioral symptom clusters among survivors of early-stage breast cancer: Development and validation of a predictive model

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2023 ASCO® ANNUAL MEETING

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Study population: the CANTO cohort

CANTO (CANcer Toxicities Cohort; NCT01993498)

- Prospective longitudinal cohort started in 2012
- 26 French cancer centers
- Dedicated network sponsored by UNICANCER
- Included over 13000 patients so far
- Ongoing inclusion: age<45; novel therapies; lung cancer

Inclusion criteria:

- 18+ years old diagnosis
- Stage I-II-III breast/lung cancer
- Untreated at time of inclusion

	Baseline	Follow-up after diagnosis					Long-term follow-up yearly for 5 years
Collected Information	**Diagnosis, pre-treatment**	**Year-1**	**Year-2**	**Year-3**	**Year-4**	**Year-6**	
Inclusion criteria							**Prolonged and long-term toxicity** **Survival Outcomes**
Signed informed consent							
Clinical examination							
Behavioral factors							
Paraclinical examination							
Questionnaires (PROs)*							
Biological samples							

Completion of primary treatment
(surgery, chemo, or radio)

*EORTC-QLQ C30, BR23, FA12, GPAQ-16, HADS, SF-12, IOCv2, social and financial reports

Vaz-Luis I et al. ESMO Open. 2019

Methods: outcome assessment

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Did you need to rest?	1	2	3	4
12. Have you felt weak?	1	2	3	4

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Giesinger JM,J Clin Epid 2020; Zigmond AS, Acta Psy 1983

Methods: outcome of interest and statistical analysis

Outcome of interest: The proportion of patients reporting a cluster of **≥3 severe CRBS** (EORTC QLQ-C30/HADS) 4 years post-diagnosis. Clinical, behavioral, treatment-related predictors, genetic risk score, and the baseline **Behavioral Symptoms Score** (BSS; based on the number of severe CRBS as proxy of **symptom burden** at diagnosis) were tested in a training cohort (Mar 2012 - Feb 2015). Performance was externally validated in patients from a subsequent enrolment period (Mar 2015 - Apr 2018).

Statistical analysis:

Model development

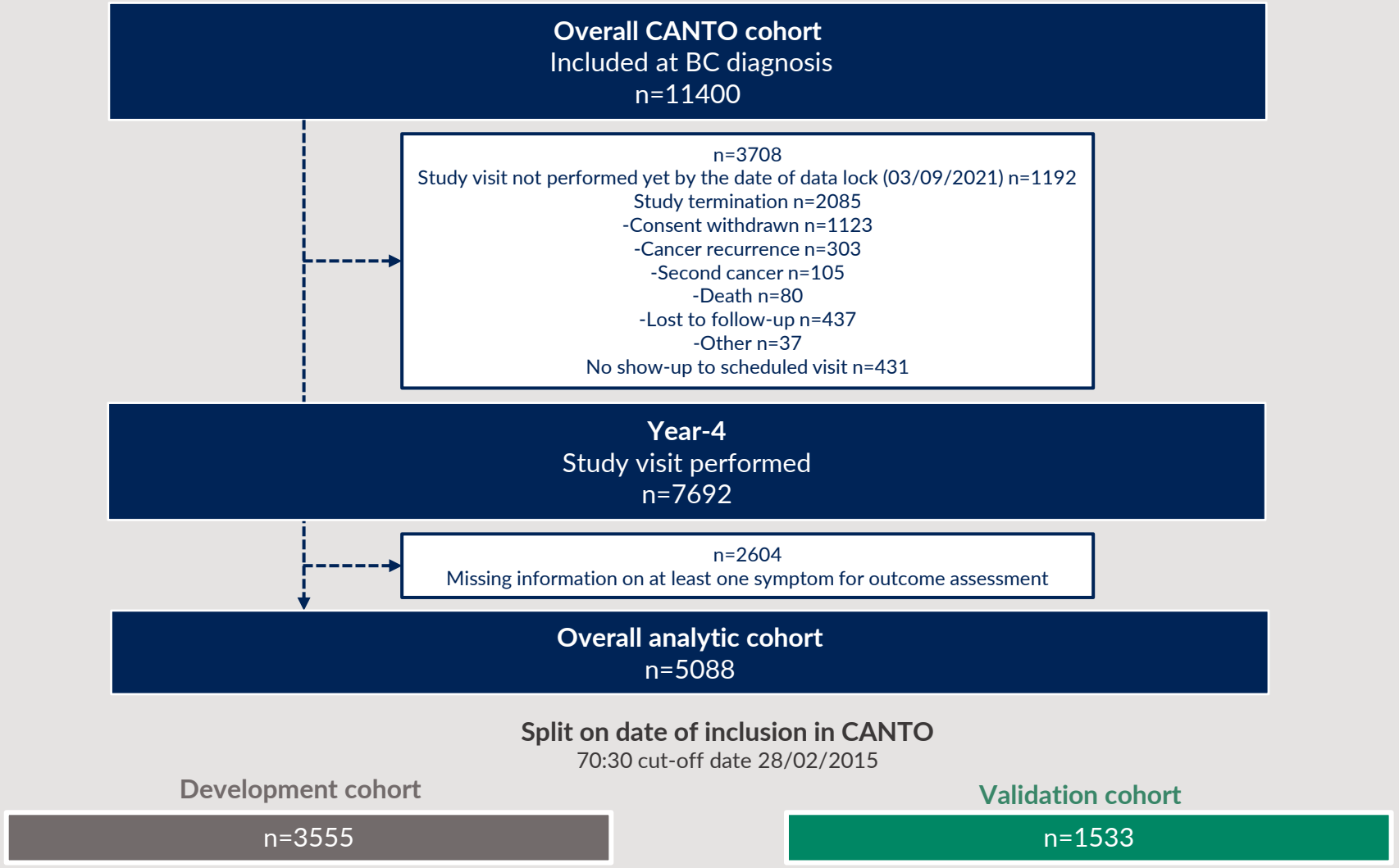
Multivariable logistic regression models identified covariates that were associated with severe CRBS 4 years post-diagnosis. A bootstrapped Augmented Backwards Elimination (ABE) procedure retained in the final model, among all available covariates, those that met a pre-specified p-value of <0.05.

Model validation

Internal: 10-fold internal cross-validation and subtraction of an over-optimism penalty from the AUC.

External: Model performance was assessed among patients from the latest CANTO data lock that had not been included in the development cohort.

Final analytic cohort



Results: key population characteristics

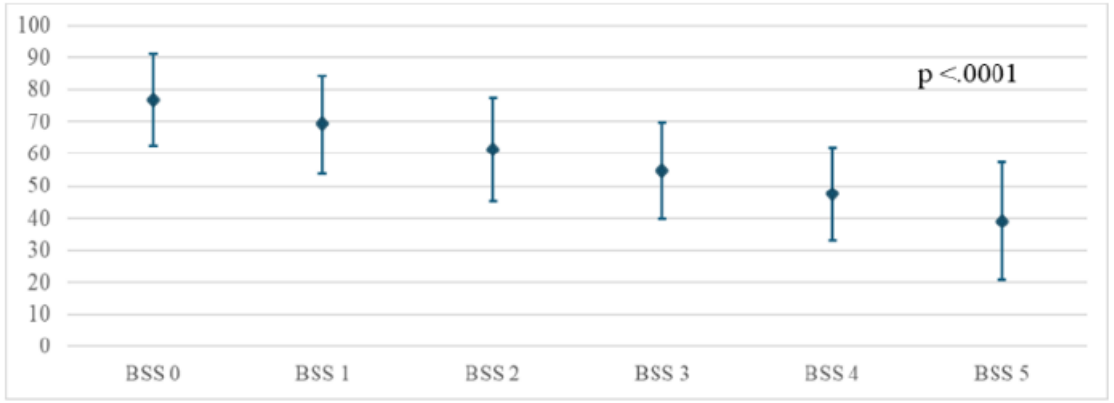
	Whole cohort n=3555	No CRBS cluster n=2800	CRBS cluster n=755
Age at diagnosis, years			
Mean (SD)	56.43 (10.9)	56.9 (10.9)	54.7 (10.7)
Menopausal status			
Premenopausal	1329 (37.6)	1000 (36.0)	329 (43.7)
Charlson comorbidity index			
0	2701 (81.7)	2152 (82.3)	549 (79.3)
≥ 1	605 (18.3)	462 (17.7)	143 (20.7)
Household income, Euros per month			
< 1,500	424 (12.8)	335 (12.8)	89 (12.8)
≥ 1,500 to < 3,000	1391 (42.0)	1070 (40.9)	321 (46.1)
≥ 3,000	1496 (45.2)	1210 (46.3)	286 (41.1)
Tobacco use behavior			
Current smoker	529 (15.1)	375 (13.6)	154 (20.7)
Former smoker	739 (21.2)	573 (20.8)	166 (22.3)
Never smoker	2224 (63.7)	1801 (65.5)	423 (56.9)
Physical activity according to WHO recommendations			
Insufficiently active	1460 (42.7)	1152 (42.6)	308 (43.3)

	Whole cohort n=3555	No CRBS cluster n=2800	CRBS cluster n=755
History of psychiatric disorders*			
Yes	535 (15.6)	380 (14.0)	155 (21.4)
Tumor stage			
Stage I	1792 (50.8)	1441 (51.7)	351 (47.1)
Stage II	1456 (41.2)	1129 (40.5)	327 (43.9)
Stage III	282 (8.0)	215 (7.7)	67 (9.0)
Axillary surgery			
Dissection	1390 (39.1)	1066 (38.1)	324 (42.9)
Breast cancer surgery			
Mastectomy	909 (25.6)	701 (25.0)	208 (27.5)
Chemotherapy			
Yes	1871 (52.6)	1442 (51.5)	429 (56.8)
Radiotherapy			
Yes	3237 (91.1)	2564 (91.6)	673 (89.3)
Endocrine therapy			
Yes	2914 (82.0)	2267 (81.0)	647 (85.7)

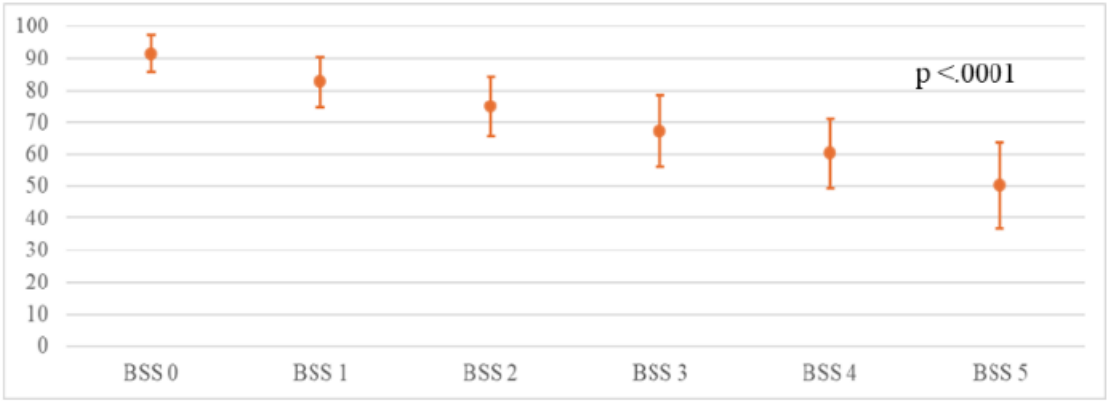
*57% depression, 20.9% anxiety, 11.4% anxiety-depressive syndrome, 5.2% sleep problems, 1.5% manic-depressive disorder, 1.1% eating disorders, 0.7% drug or alcohol addiction, 0.7% burn-out, 0.6% self-harm, 0.4% post-traumatic stress disorder.

Results: global quality of life according to BSS

GHS/QoL values according to BSS at year-4
EORTC QLQ-C30 items 29 and 30



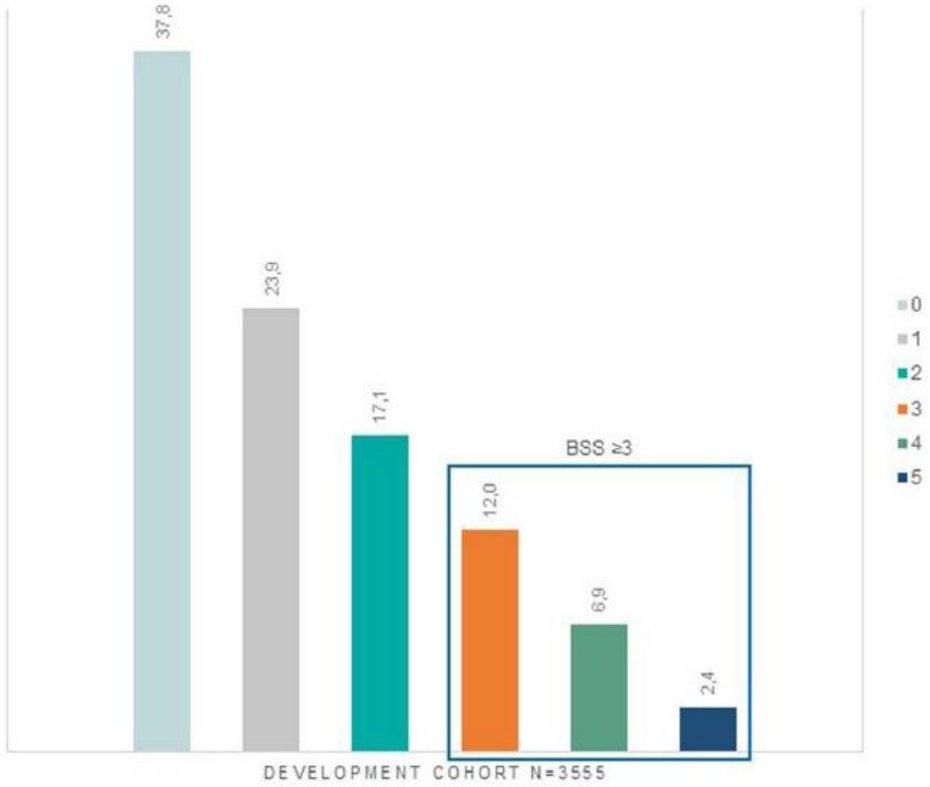
C30 Summary score according to BSS at year-4
mean of 13 out of 15 EORTC QLQ-C30 scales



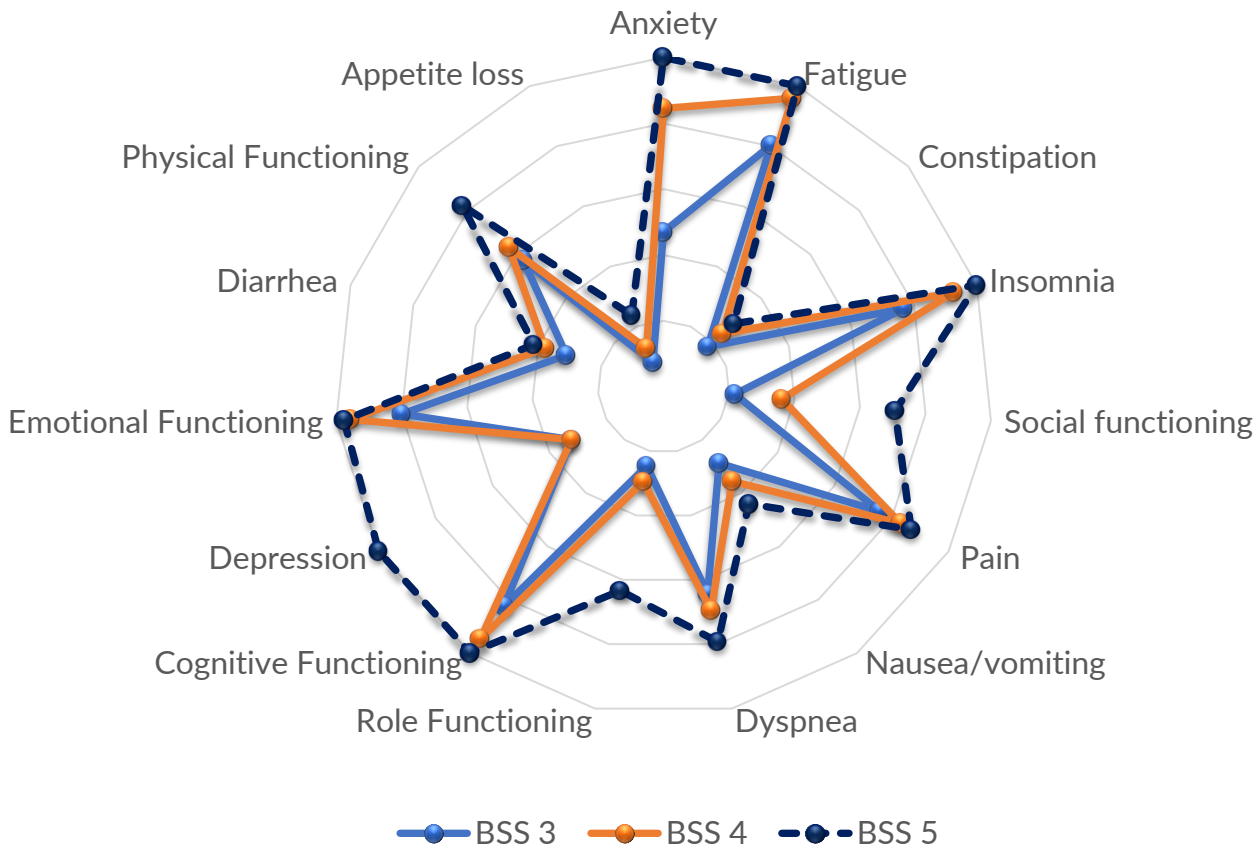
Continuous global quality of life scores according to BSS.
Diamonds and dots describe mean scores. Error bars indicate 95% Confidence Intervals for mean scores. p-values from Kruskal-Wallis test.

Results: prevalence of symptoms

Patients reporting ≥3 severe behavioral symptoms 4 years post-diagnosis

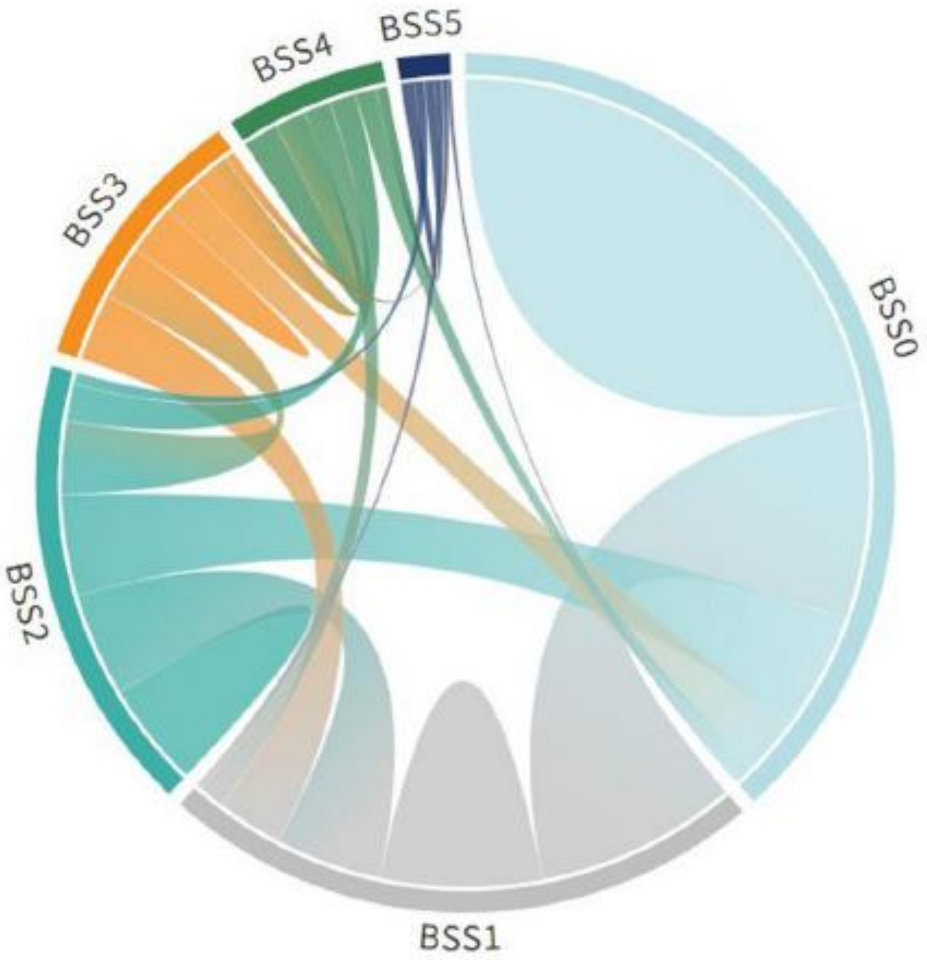


Prevalence of severe CRBS and other severe symptoms and impaired functions assessed by the EORTC QLQ-C30 items 4 years after breast cancer diagnosis



Results: flows between BSS at diagnosis and BSS at year-4

The thickness of the arcs is proportional to the magnitude of the flow in each group. The table displays the proportion of patients in each flow.



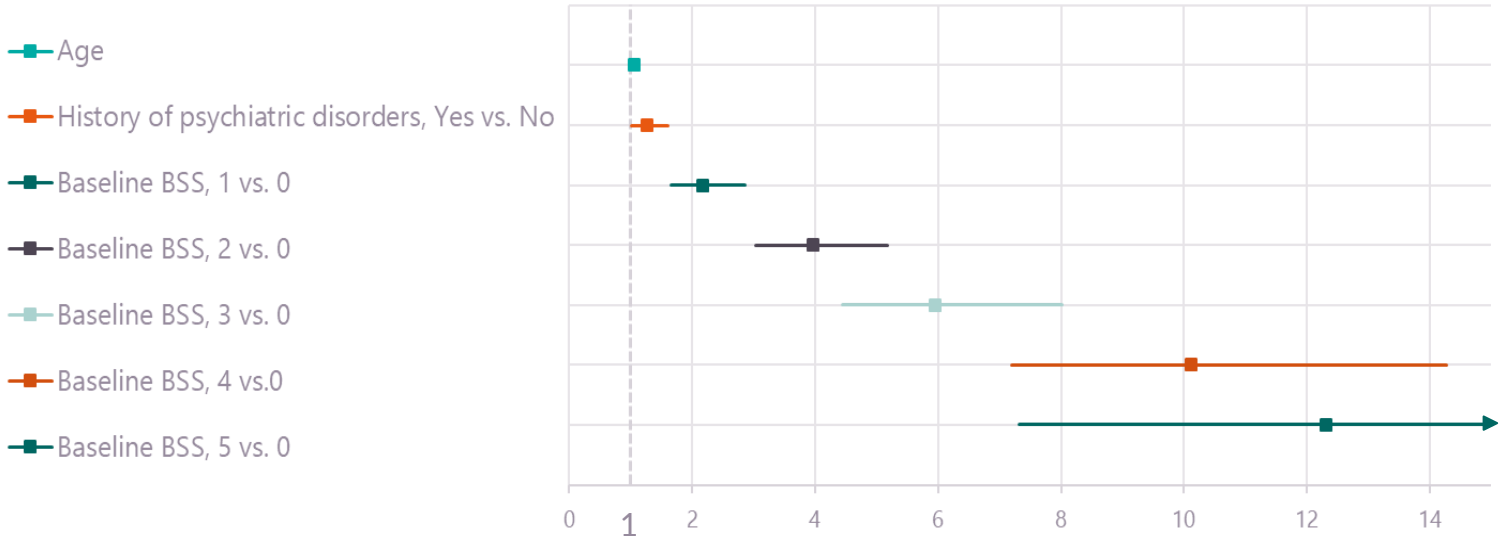
Diagnosis \ Year-4	BSS	0	1	2	3	4	5
	0 (n=1337)	764 (57.1%)	301 (22.5%)	160 (12.0%)	82 (6.1%)	24 (1.8%)	6 (0.5%)
	1 (n=794)	283 (35.6%)	226 (28.5%)	148 (18.6%)	93 (11.7%)	37 (4.7%)	7 (0.9%)
	2 (n=603)	141 (23.4%)	145 (24.1%)	147 (24.4%)	102 (16.9%)	52 (8.6%)	16 (2.7%)
	3 (n=360)	54 (15.0%)	95 (26.4%)	74 (20.6%)	70 (19.4%)	53 (14.7%)	14 (3.9%)
	4 (n=212)	29 (13.7%)	37 (17.5%)	37 (17.5%)	44 (20.8%)	49 (23.1%)	16 (7.6%)
	5 (n=70)	5 (7.1%)	11 (15.7%)	14 (20.0%)	8 (11.4%)	14 (20.0%)	18 (25.7%)
	Total	1276	815	580	399	229	77

The concordance between the baseline BSS and reporting a cancer-related behavioral symptom cluster 4 years after diagnosis was low (Cramer V¼0.25).

Results: predictive model of the risk of CRBS clusters 4 years after diagnosis

Adjusted§ predictive model of CRBS clusters 4 years post-dx.		
Predictor	**Prevalence at diagnosis (%)**	**Odds Ratio (95% CI)**
Age		
Mean (SD)	56.4 (10.9)	1.06 (1.02-1.11)*
Previous psychiatric disorders		
No	84.4	Ref
Yes	15.6**	1.27 (1.01-1.60)
Baseline BSS		
0	39.6	Ref
1	23.5	2.17 (1.66-2.85)
2	17.8	3.96 (3.04-5.18)
3	10.7	5.96 (4.44-8.02)
4	6.3	10.11 (7.19-14.26)
5	2.1	12.30 (7.33-20.87)

§by all predictors + BMI, comorbidities, neurological disorders, socioeconomic, alcohol, tobacco, exercise, local and systemic tx.
*for 5-years decrease.
**56.6% depression, 21.1% anxiety, 11.2% anxiety-depressive syndrome, 5.4% sleep problems, 1.5% manic-depressive disorder, 1.1% eating disorders, 0.8% drug or alcohol addiction, 0.7% burn-out, 0.6% self-harm, 0.4% post-traumatic stress disorder.



Clinical implementation: risk assessment tool

	Scenario 1	Scenario 2
Age	60	35
History of psychiatric disorder	No	Yes
Baseline BSS	1	5
Individual risk	3%	65%

Discussion

Key findings of the study

- **about 1 in 5 patients** with early- stage breast cancer reported a **cluster of 3 or more severe CRBS 4 years after diagnosis**
- **younger patients** with a medical history of **psychological or psychiatric disturbance** and a **higher pre-treatment symptom burden** had greater risk of long-term CRBS
- **more than half of the patients** presenting with a long-term CRBS cluster had reported **fewer than 3 symptoms at baseline** (need for continuous monitoring and proactive provision of supportive measures!)

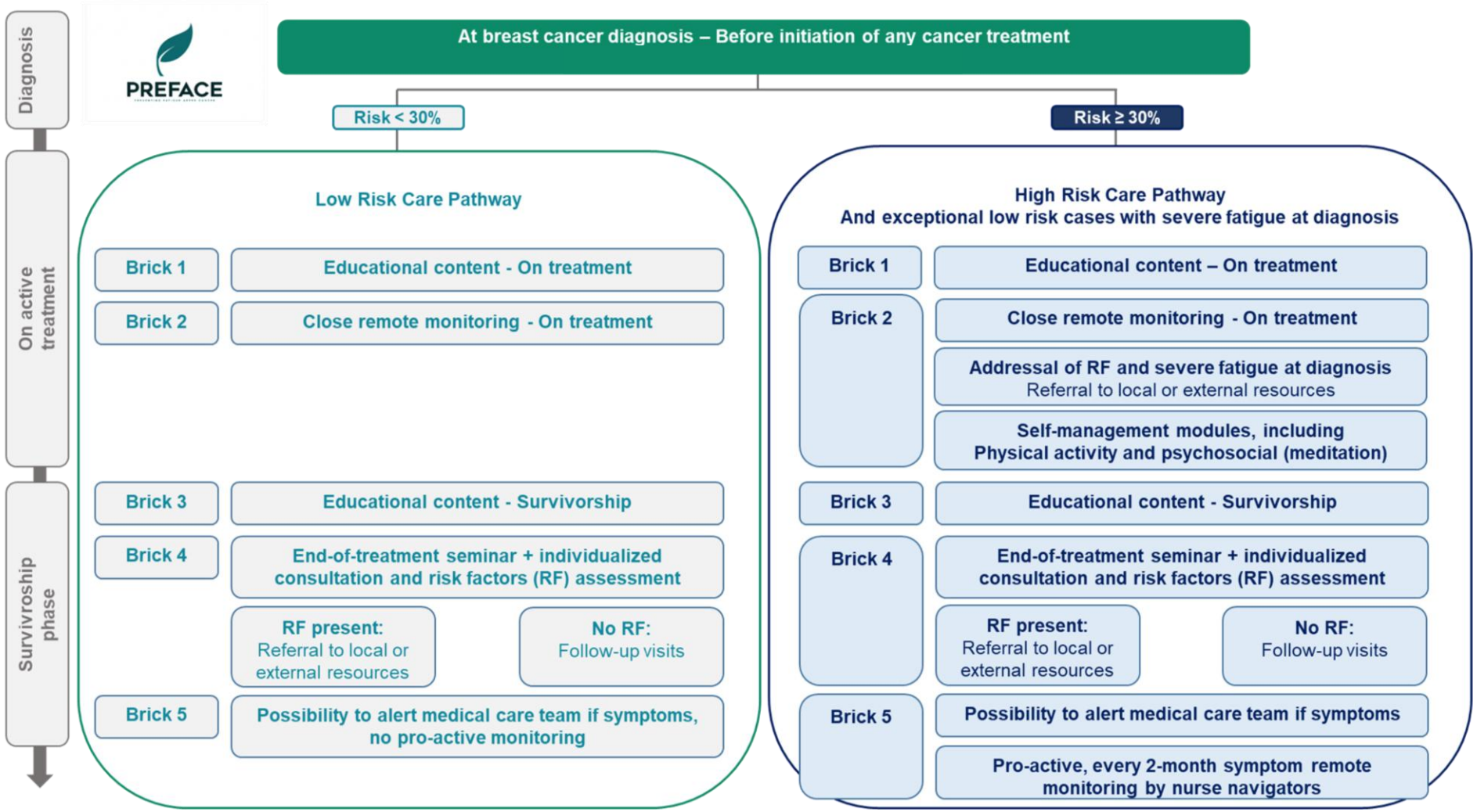
Study limitations

- **potential bias** from study termination for patients experiencing disease recurrence or death
- generalization to different tumor populations as well as to ethnically diverse populations may be limited

Implication for clinical practice and future research directions

- our predictive model can aid risk stratification of patients diagnosed with early-stage breast cancer, which can result in facilitating referrals to pre-habilitation or management interventions for long-term CRBS clusters
- **systematic screening** of medical history and symptoms **at diagnosis of breast cancer** is crucial for the prediction of long-term CRBS and may help clinical management
- **PROs** enable to identify patients experiencing significant initial symptom burden and who are perhaps most in need of **personalized supportive care** from the time of their breast cancer diagnosis

Clinical implementation: PREventing Frailty After breast canCEr



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