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Journal

Psycho-Oncology, 27(2)

ISSN

1057-9249

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Publication Date

2018-02-01

DOI

10.1002/pon.4472

Peer reviewed

HHS Public Access

Author manuscript

Psychooncology. Author manuscript; available in PMC 2019 May 22.

Published in final edited form as:

Psychooncology. 2018 February ; 27(2): 420–426. doi:10.1002/pon.4472.

Predicting Future Major Depression and Persistent Depressive Symptoms: Development of a Prognostic Screener and PHQ4 cutoffs in Breast Cancer Patients

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Abstract

OBJECTIVE: Create a brief, self-report screener for recently diagnosed breast cancer patients to identify patients at risk of future depression.

METHODS: Breast cancer patients (N = 410) within 2 ± 1 months after diagnosis provided data on depression vulnerability (DV). Depression outcomes were defined as a high depressive symptom trajectory or a major depressive episode during 16 months after diagnosis. Stochastic gradient boosting of regression trees identified seven items highly predictive for the depression outcomes from a pool of 219 candidate DV items. Three of the seven items were from the PHQ-4, a validated screener for current anxiety/depressive disorder that has not been tested to identify risk for future depression. Thresholds classifying patients as high or low risk on the new Depression Risk Questionnaire-7 (DRQ-7) and the PHQ-4 were obtained. Predictive performance of the DRQ-7 and PHQ-4 was assessed on a holdout validation subsample.

FINDINGS: DRQ-7 items assess loneliness, irritability, persistent sadness, and low acceptance of emotion as well as three items from the PHQ-4 (anhedonia, depressed mood, worry). A DRQ-7 score of ≥6/23 identified depression outcomes with 0.73 specificity, 0.83 sensitivity, 0.68 PPV and 0.86 NPV. A PHQ-4 score of ≥3/12 performed moderately well but less accurately than the DRQ-7 (net reclassification improvement =10%; 95% CI [0.5 – 16]).

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The authors have no conflicts of interest.

INTERPRETATION: The DRQ-7, and the PHQ-4 with a new cutoff score, are clinically accessible screeners for risk of depression in newly diagnosed breast cancer patients. Use to select patients for preventive interventions awaits validation of the screener in other samples.

Keywords

Oncology; Depressive Disorder; Depressive Symptoms; Breast Cancer; Prognostic; Risk; Screener; Emotion Acceptance

Prevention and treatment of depression are vital for optimal cancer survivorship. In breast cancer patients, the prevalence of depressive disorders triples during breast cancer treatment, as compared to demographically similar community women, and mortality risk increases[1] via mechanisms that are beginning to be understood.[2] Persistent depressive symptoms and major depressive episodes (MDE) in breast cancer survivors are linked to poor medical regimen adherence and unhealthy behaviors[3,4] delayed return to work[5], higher healthcare use, costs and depression associated hospitalizations, [6]as well as increased suicide [7]. Although valid methods for identification and treatment of cancer patients with *current* depressive disorders are available[8,9], there are no clinically practical approaches to screening for risk of *future* depression to facilitate preventive interventions. Walker et al.[10] demonstrated that screening followed by treatment of cancer patients with MDE is feasible and cost effective, setting the stage for a parallel effort to detect and intervene with patients at elevated risk to prevent depressive disorders.

Studies of preventive interventions for depression for individuals at risk are promising. A meta-analysis of 32 studies found a 21% reduction in depressive disorders after intervention as compared to control conditions[11]. The indicators of risk in these studies were the presence of a medical illness or another significant stressor (selective prevention) or elevated depressive symptoms (indicated prevention). The number needed to treat was 20 intervention participants for each depressive disorder prevented.

PredictD was the first prognostic algorithm for onset of major depression over 12 months[12] (C-statistic 0.79 [0.77–0.81]). The feasibility of PredictD in clinical practice may be limited by its length (35 questions), as would the other published algorithm for calculating risk for first-onset depressive disorder[13]. Also, a recent publication cautioned “the use of PredictD in the US general population for predicting individual risk of MDE is not encouraged” due to calibration problems[14].

Recent longitudinal cohort studies show vulnerability to depression increases over time with successive episodes of MDE and point to an opportunity to prevent this self-perpetuating cycle[15]. Vulnerability to clinically significant depression varies substantially among women with breast cancer, depending on specific macro-level and sociodemographic factors; disease and treatment contexts; intrapersonal factors; interpersonal contexts; and emotional and cognitive dysregulation diatheses[16] Despite this rich knowledge base, risk factors have not been comprehensively examined for their predictive ability. The objective of this project was to use data from a longitudinal study of breast cancer patients to create a brief, self-report prognostic screener for depression [Depression Risk Questionnaire (DRQ)]) that is feasible for clinical practice.

Method

This project is a component of the MYA (My Year After breast cancer) study, a prospective, longitudinal investigation of a theory[17] and evidence based[15,18] model (Figure 1) for risk of depression during 16 months following breast cancer diagnosis.

Data were collected from April 2010 to September 2014. Consecutive patients were identified at three community oncology clinics in Los Angeles and at the University of Arizona Cancer Center in Tucson. Eligibility criteria were: new diagnosis or first recurrence/second primary of invasive breast cancer (Stage I-IV), study entry within four months of diagnosis, and English literacy. Any standard medical treatment for cancer was allowed. Exclusion criteria were < 21 years and bipolar, psychotic or neurocognitive disorder. The University of Arizona Human Subjects - Protocol Number 0900000382R005 and the UCLA Human Research Protection Program -IRB#16–000878 approved the study. Patients provided written informed consent.

A total of 460 women had assessments at study entry (2.1 ± 0.8 months after diagnosis) and 6, 12, 18, 24, 36, and 52 weeks thereafter. Fifty women were excluded from analyses, 3 due to insufficient outcome data and 47 because of low depressive symptoms in the context of depression treatment at study entry, potentially decoupling risk indicators from depressive outcomes prevented by treatment. The remaining 410 women were divided into model development and validation samples based on enrollment date (≤ 16 January 2013, n = 328 and > 16 January 2013, n = 82). Such non-random splits are one of the strongest study designs (Type 2b) for development of prognostic indices, according to the TRIPOD statement[19]. Because no model fitting occurs on the validation data, a relatively small sample size is sufficient to evaluate the accuracy of the screening model. SDC-Figure 1 shows participant flow.

Depression Outcome

Major depressive disorder [Composite International Diagnostic Interview (CIDI)[20]] and depressive symptoms [Center for Epidemiologic Studies-Depression scale (CES-D)[21]] were assessed seven times over twelve months. A growth mixture model was fit to the longitudinal CES-D measurements as previously described[22], which identified four depressive symptom trajectory patterns or classes: high, recovery, low, and very low. Consistently elevated depressive symptoms characterized the high trajectory class. For each woman, the model provided probability of membership in each trajectory class. A probability threshold of .33 captured all women for whom the high trajectory was the highest of the four trajectory probabilities. SDC-Figure 2 illustrates this natural break in the distribution of probabilities for trajectory class membership. Women were classified as experiencing a depression outcome if they experienced a MDE or were in the high CES-D trajectory class. Sixteen percent developed a major depressive episode and 38% were estimated to have chronically elevated depressive symptoms over 16 months after diagnosis[22].

Candidate Items

Eight categories of risk for depression (A – H in Figure 1) were assessed using 42 self-report scales plus descriptive characteristics (219 items): 1) general depressive diatheses (history of depression, neuroticism, early adversity, loneliness, marital dysfunction), 2) emotion dysregulation (emotion acceptance, emotion regulation, suppression, reappraisal, attachment security), 3) coping (emotion expression and processing, seeking support, acceptance, behavioral and mental disengagement, denial, problem solving), 4) Non-cancer stressors, 5) cancer severity and treatments (multiple items), 6) physical health problems (neuropathy, insomnia, pain, fatigue, number of comorbid diseases, other breast cancer adverse effects), 7) psychological health (depression/anxiety symptoms, intrusive thoughts, positive emotions, substance abuse, satisfaction with life) and 8) demographics[22]. Measures for each risk characteristic are in SDC Sections A and C and SDC-Table 1.

Statistical Methods

We used high-performance prediction modeling to identify a small set of items that were highly predictive of the depression outcomes. Model development and validation are summarized here, with details in SDC-Section B. Missing data were multiply imputed using bagged trees[23] to generate 25 imputed datasets separately for the development and validation samples. All performance metrics and tests were conducted on the multiply imputed data. Pooled results are reported. Multiple imputation and prediction models were conducted using the R packages caret[24] and gbm[25].

Development.—The prediction model was created on the development sample using stochastic gradient boosting of classification trees (“GBM”). GBM is a machine learning technique that produces a prediction model as an ensemble of many classification and regression trees, iteratively trained; cases misclassified at one iteration are given greater weight during later iterations[26,27]. See Adams, Bello and Dumancas[28] for an example of predictive modeling.

A detailed description of the analytic steps to select the best set of items for the screener can be found in SDC-Section B. Briefly, after optimizing the tuning parameters to get the best fitting model, the GBM yielded variable importance values used to rank the items. To choose the number of items for the screener, we examined the performance (accuracy, kappa, sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) of models that used the top 2–10, 15, 20 or 30 items and weighed incremental performance differences against the burden of additional items. Performance metrics for full and reduced item sets (See SDC-Section A for details) were used to select the smallest number of items without substantial loss of performance. After the final number of items was selected, we fit a logistic model (“GLM”) using these items to develop a simple summation scoring method suitable for a brief screener.

To classify individuals as high or low risk for the depression outcome, we selected a threshold of PPV≈0.80 *a priori* consistent with our goal of developing a prognostic screener in order to allocate potentially limited intervention resources effectively (i.e., if a woman screens positive, she has a high probability of it being a true positive). For the GBM and

GLM, we used predicted probability thresholds and for the brief screener we used integer-valued thresholds corresponding to PPVs of 0.80. Performance metrics were calculated for the development sample using these thresholds. McNemar tests were conducted to assess whether the methods classified the same women differently.

Validation.—The models and thresholds derived from the development process were applied to the holdout validation sample to evaluate performance.

Results

The mean age of subjects was 56 (±12) years. Nineteen percent were Latina, 5% Asian, 2% each African American and American Indian, and the rest European American Caucasian. Most had some college education (75%), were married (67%), and employed (52%). Most had early-stage breast cancer (stages 1, 2, 3, 4: 44%, 39%, 11%, 5%, respectively) and surgery, chemotherapy, and endocrine therapy during the study[22]. Women in the development and validation samples were not significantly different on demographic characteristics. In the development (validation) samples, 17% (17%) experienced an MDD, 47% (41%) were in the high trajectory class, and 51% (41%) experienced one or both of these depression outcomes (SDC-Table 2). Mean CES-D scores were 17.6±7.3 for women with depression outcomes and 5.1±3.4 for the others (SDC -Figure 3).

Development

Gradient boosting modeling (GBM) yielded a ranking of items by their importance for predicting the depression outcome. Using the top 7 items for the DRQ-7 balanced near optimal performance with brevity, as ascertained by varying the number of top-performing items used for prediction and calculating performance measures. SDC-Figure 4 shows improvement in prediction with each additional item up to 7 and then no substantial improvement when adding items up to a total of 30 and beyond. Table 1 lists the coefficients for weighted scoring of the sum of these items. Table 2 shows how the original item scorings were harmonized and simplified to create the DRQ-7 screener, with further explanation of item scoring in SDC-section C.

The DRQ-7 included three of the four PHQ-4 items, suggesting our objective of developing a screener might be met by identifying a new threshold score on the PHQ-4, thereby eliminating the need to introduce a new tool for clinical use. Therefore, we did subsequent analyses with both the DRQ-7 and the PHQ-4, and tested for performance differences. Thresholds to achieve PPV ≈ 0.80 were ≥6 for DRQ-7 and ≥3 for PHQ-4. The DRQ-7 performed well (C-statistic = .83); the PHQ-4 performed slightly less well (C-statistic = .79). SDC-Table 3A shows model performance including threshold, C-Statistic, accuracy, kappa, sensitivity, specificity, PPV, and NPV for both scales. McNemar tests showed significantly different classification with the DRQ-7 and the PHQ-4 (p = .005). Results for thresholds achieving maximum accuracy favored the DRQ-7.

Model performance in the development sample was reexamined excluding women with PHQ-9 ≥10 at study entry (n=59). While sensitivity was reduced, overall the model still performed well with C-statistic of .80, accuracy .75, sensitivity .66, and specificity .81.

Validation

The developed screening models and thresholds were applied to the validation sample (N = 82). Performance metrics are shown in Table 4 (SDC-Table 4A shows performance for additional models, SDC-Table 4B shows performance using thresholds maximizing accuracy and SDC-Table 4C shows performance for the PHQ-4 including thresholds suggestive of current major depression). The DRQ-7 performed well in the validation sample with C-statistic 0.85, accuracy 0.77, sensitivity 0.83, specificity 0.73, PPV 0.68 and NPV 0.86. The receiver operating curves (ROC) are shown in SDC-Figure 5 for the development and validation subsamples.

Post-Hoc Analyses - Net Reclassification Improvement

Comparison of the DRQ-7 with the PHQ-4 to classify women on depression outcomes for the full sample were calculated with bootstrapped 95% confidence intervals using the net reclassification improvement (NRI) index. The NRI[29] quantifies the total improvement in the classification of depression outcomes when the 4 items of the DRQ-7 are added to items from the PHQ-4 contained within the DRQ-7.

Net reclassification improvement (NRI) favored the DRQ-7 over the PHQ-4 for the sample overall (7.8% [0 – 15.5]) and for subjects with depression outcomes (10.2% [4.5–15.9]), but not for subjects without depression outcomes (−2.4% [−7.7, 2.5]). See SDC-Table 5.

Selection of Thresholds

Although we used a threshold sum score of 6 for the DRQ-7, depending on the desired sensitivity and specificity, alternate thresholds may be used. Figure 5 in the SDC shows the tradeoff between sensitivity and specificity for threshold sum scores ranging from zero to 22 on the DRQ-7. For example, cut offs of >5/23 or ≥7/23 instead of >6/23 would increase or decrease sensitivity, respectively (.84 or .60 vs .74) and change specificity (.60 or .85 vs . 75), resulting in a larger number of patients identified at risk with more false positives and fewer false negatives using ≥5/23 and a smaller number of patients identified at risk using ≥7/23 with fewer false negatives and more false positives.

Discussion

We developed and conducted initial validation of the DRQ-7, a prognostic screener for identification of women at risk for persistently elevated depressive symptoms or MDD during 16 months following breast cancer diagnosis. The 7 items were selected from a pool of over 200 items in measures of vulnerability to depression.

The DRQ-7 contains 3 of the 4 items from the PHQ-4[30], a screener validated for current depressive and anxiety disorders. Therefore, we established prognostic thresholds for the PHQ-4 in our samples using the same prediction modeling methods as for the DRQ-7. This new threshold for the PHQ-4 (≥3/12) performed well, but the DRQ-7 demonstrated higher accuracy as indicated by net reclassification improvement[29] of ten percent. This means screening with the DRQ-7 correctly predicts depression outcomes for an additional 10% of subjects compared to the PHQ-4.

The PHQ-4 item that is not in the DRQ-7 (Feeling nervous, anxious or on edge) does not add substantially to classification in this sample. However, another item indexing anxiety from the GAD-7 (Becoming easily annoyed or irritable) (Supplement Ref 9) was among the DRQ-7 items. This indicates irritability is a stronger risk indicator than feeling nervous, anxious or on edge among these breast cancer patients. Past history of MDD is an established risk factor for future MDD, yet it was not empirically selected. Post-hoc analyses demonstrated a high correlation of PHQ-4 symptoms with past MDD (r=−.61), indicating the PHQ-4 items capture the risk associated with history of MDD for purposes of this screener.

The DRQ-7 items that quantify symptoms of depressed mood, anhedonia and worry are known to be malleable with available interventions[31]. The items measuring loneliness, persistent sadness, and acceptance of emotions quantify vulnerabilities that are thought to be more enduring; however, recent interventions suggest they are malleable[32] and variation in depression vulnerability over time in recent cohort studies supports this view[15]. Thus, risk processes tapped by the DRQ-7 show promise as targets for preventive interventions.

To our knowledge, the only published trial of selective or indicated preventive intervention for MDD in cancer patients studied a brief nurse-delivered intervention that reduced the incidence of MDD among high-risk patients (previous mental health treatment or ≥ 8/56 cancer-related concerns score) compared to wait-list controls. The intervention had no significant impact among low-risk subjects[33]. This demonstrates the value of a screener to identify individuals at significant risk as the targets for preventive interventions.

Limitations and Strengths

The DRQ-7 is not a purely predictive screener, as we did not exclude women with elevated symptoms or MDD at study entry from the sample. Four subjects met criteria for MDE at study enrollment and they were also in the high trajectory group throughout the next 12 months. Our pragmatic aim was to produce a prognostic screener for use in the first few months after breast cancer diagnosis (near the usual onset of adjuvant therapy), and exclusion of these subjects would have eliminated part of the high-risk group. Clinical settings aiming to separate subjects with current depressive disorders from those at risk for depression in the next year could administer the DRQ-7 or the PHQ-4 and score the PHQ-2 items (included in the DRQ-7 and the PHQ-4) using established thresholds for current MDD[34].

Participants were recruited from two geographic areas to increase heterogeneity; however, the findings may not generalize to all recently diagnosed breast cancer patients, and its use in men and for patients with other types of cancer awaits study. Although we made efficient use of the sample to cross-validate the DRQ-7, the sample size was limited due to time and cost constraints. Validation should be considered preliminary pending a larger validation study. The study also had notable strengths. We used a theoretically and empirically grounded framework to comprehensively assess risk and protective factors for depression in women with breast cancer. We used one of the strongest study designs (Type 2b) according to the TRIPOD statement, making a non-random split of the sample to provide preliminary

evidence that the DRQ-7 performs well in data not used for development and generalizes across time[19].

Clinical Implications:

Prospective studies of risk for depression after breast cancer diagnosis have established a strong evidence base for individual risk indicators. However, this knowledge has not been translated to produce an efficient and accurate screener to identify the subset of women who are most likely to benefit from preventive interventions. These results indicate that the DRQ-7 and the PHQ-4 warrant further study for this task. Which scale to use in an individual clinic may be informed by the pragmatics of current practice and the perceived importance of 10% increased classification accuracy with the DRQ-7 vs. the PHQ-4.

Conclusions:

Accurate identification of individuals at risk can maximize the benefits of limited therapeutic resources. The DRQ-7 and a new PHQ-4 cutoff score were developed as practical tools to identify patients at risk for clinically significant depression in the year after breast cancer diagnosis. They compare favorably with PredictD, a well-validated algorithm for stratifying primary care patients for depression risk over 24 months. Validation in a larger sample, and in other cancer types, will set the stage for selecting and targeting patients for interventions to prevent depression after cancer diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Supported by NIH R01 CA133081 (Stanton & Weihs, co-PIs); Breast Cancer Research Foundation (Stanton, PI); NCI-NIH P30CA023074 (Alberts, PI); NCI-NIH P30 CA 16042 (Crespi, PI: Dorshkind)

Abbreviations:

CES-D	Center for Epidemiologic Studies Depression Scale
DV	Depression Vulnerability
DRQ-7	Depression Risk Questionnaire 7
GBM	Stochastic gradient boosting of classification trees machine
GLM	General logistic model
MDD	Major Depressive Disorder
MYA	My Year After cancer study
NPV	Negative Predictive Value
NRI	Net reclassification improvement

PHQ-4/9	Patient Health Questionnaire 4/9
PPV	Positive predictive value
SDC	Supplemental Digital Content

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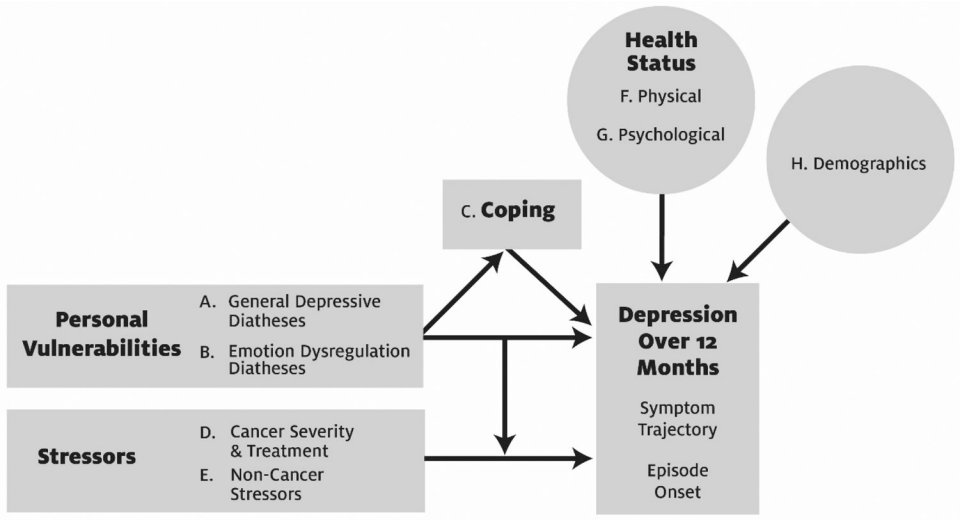

Figure 1.
Theoretical model for depression vulnerability

Table 1.

Final selected screener items ordered by relative importance in the development sample

Scale	Item	GBM model: relative importance	GLM model: logistic regression coefficient
UCLA Loneliness[35]	How often do you feel unhappy doing so many things alone? (LON)	6.37	.258
PHQ – 9[36]	Little interest or pleasure in doing things. (INT)	5.63	.372
PHQ – 9	Feeling down, depressed, or hopeless. (DEP)	5.54	.364
GAD – 7[37]	Not being able to stop or control worrying (WOR)	5.36	.445
NEO-Neuroticism[38,Note]	I am seldom sad or depressed. (NEU)	4.74	−.408
GAD – 7	Becoming easily annoyed or irritable (IRR)	3.81	.226
Acceptance of Emotion[39]	I understand and like my feelings just as they are. (ACC)	2.95	−.439

Note. Relative importance values are from GBM model using the full item set. Coefficients are from logistic regression for the top seven items in the development sample per standard deviation change in each predictor. Results are averages across 25 multiply imputed datasets. Unstandardized GLM regression = .911 + .306(LON) + .480(INT) + .501(DEP) + .538(WOR) −.343(NEU) + .282(IRR) −.172(ACC).

Note. "I seldom feel blue", from the International Personality Item Pool (correlated ·82 [·92 after correction for unreliability][36,40]with NEO) was substituted in the DRQ-7 for copyright purposes.

Table 2:

DEPRESSION RISK QUESTIONNAIRE (DRQ-7) for newly diagnosed breast cancer patients

Indicate how well each statement describes you in relation to your feelings:					
	Strongly agree	Mostly agree	Equally agree and disagree	Mostly disagree	Strongly disagree
I understand and like my feelings just as they are	0	1	2	3	4
I seldom feel blue	0	1	2	3	4
Over the last 2 weeks, how often have you been bothered by any of the following problems?					
	Not at all	Several days	More than half the days	Nearly every day	
Little interest or pleasure in doing things	0	1	2	3	
Feeling down, depressed, or hopeless	0	1	2	3	
Not being able to stop or control worrying	0	1	2	3	
Becoming easily annoyed or irritable	0	1	2	3	
	Never	Rarely	Sometimes	Often	
How often do you feel unhappy doing so many things alone?	0	1	2	3	
Add Columns TOTAL:		+	+	+	

Thank you for completing this form!

Table 3.

Model performance in development and validation [95% bootstrapped CI] subsamples

Model	Threshold	C-Statistic	Accuracy	Kappa	Sensitivity	Specificity	PPV	NPV	N High	N Low
A. Development Subsample										
DRQ-7	6/23	0.83	0.77	0.53	0.76	0.78	0.78	0.76	162	166
PHQ-4	3/12	0.79	0.72	0.45	0.65	0.80	0.77	0.69	141	187
B. Validation Subsample										
DRQ-7	6/23	0.85 [0.76, 0.93]	0.77 [0.67, 0.85]	0.54 [0.34, 0.71]	0.83 [0.68, 0.95]	0.73 [0.60, 0.84]	0.68 [0.53, 0.81]	0.86 [0.74, 0.96]	41.1 [33.0, 50.0]	40.9 [32.0, 49.0]
PHQ-4	3/12	0.82 [0.72, 0.91]	0.75 [0.66, 0.84]	0.50 [0.29, 0.68]	0.74 [0.58, 0.89]	0.76 [0.63, 0.88]	0.69 [0.51, 0.83]	0.81 [0.69, 0.92]	36.8 [28.0, 46.0]	45.2 [36.0, 54.0]

PPV, positive predictive value; NPV, negative predictive value; N High/Low, number of women classified as high/low risk.