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Article

In Silico Psycho-oncology: Understanding Resilience Pathways in Breast Cancer - Determinants of Longitudinal Depression and Quality of Life Trajectories

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Abstract

Background/Objectives: Patients with breast cancer show substantial heterogeneity in psychological adjustment following diagnosis. We aimed to characterize longitudinal trajectories of quality of life (QoL) and depressive symptoms during the first 18 months post-diagnosis and to identify robust clinical, psychosocial, and behavioral predictors associated with distinct adjustment pathways. **Methods:** Data were drawn from the multicenter BOUNCE cohort. QoL (EORTC QLQ-C30) and depressive symptoms (HADS) were assessed repeatedly over 18 months. Latent Class Growth Analysis and Growth Mixture Modeling were used to identify distinct trajectory classes. Associations between candidate predictors and trajectory membership were examined using logistic regression combined with elastic net regularization, including clinically motivated binary contrasts. Predictor robustness was evaluated under models with clinical site alternatively penalized and unpenalized. **Results:** Depression trajectories demonstrated heterogeneity, with groups characterized by persistent resilience (59.7%), stable moderate/high depression (25.3%), delayed-onset depression (5.0%), and recovery (10.0%). QoL trajectories ranged from stable excellent (13.2%) and stable high (13.2%) functioning to persistent low or deteriorating QoL (6.9%), with a distinct recovery trajectory (7.8%). Trajectory differentiation was primarily driven by psychological resources, symptom burden, functional status, and coping processes, while selected clinical factors contributed to specific trajectories. Patterns of predictors differed across trajectory contrasts. **Conclusions:** Distinct subgroups of women with breast cancer follow divergent QoL and depression trajectories after diagnosis. Differences between trajectories are shaped by a combination of psychological, functional, and clinical factors, highlighting the multidimensional nature of resilience and recovery. These findings support the need for tailored interventions that move beyond risk reduction toward promoting long-term well-being and mental health.

Keywords: in silico medicine; in silico psycho-oncology; machine learning; artificial intelligence; breast cancer; resilience; depression; quality of life

1. Introduction

Patient resilience is a critical determinant of cancer treatment outcomes, influencing both psychological adaptation and overall quality of life [1]. Higher levels of resilience have been associated with younger age, female sex, higher socioeconomic status and being married, as well as with internal psychological resources such as optimism, self-efficacy and adaptive emotion regulation strategies and external resources such as social support [2–4]. Positive cognitive strategies, including acceptance and positive thinking, are linked to enhanced psychological well-being, whereas maladaptive strategies such as rumination and catastrophizing are consistently associated with adverse emotional outcomes [5–11]. Among women with breast cancer, optimism and self-efficacy predict better psychological well-being, improved quality of life and lower distress over time [12,13], while perceived social and family support facilitates adaptive coping and resilience [14–17].

Within this context, the EU-funded BOUNCE project (<https://www.bounce-project.eu/>; accessed 20 December 2025) conducted a prospective multicenter clinical study across Finland, Italy, Portugal and Israel to investigate predictors of resilience trajectories among women with breast cancer. The study collected a thorough range of sociodemographic, clinical, psychological and functional factors with the aim of improving the ability to predict resilience in response to breast cancer and, ultimately, to inform personalized interventions that promote effective psychological recovery.

The aim of the current study is twofold: (1) to identify distinct longitudinal trajectories of depression and quality of life (QoL) over the 18 months following diagnosis and/or surgery and (2) to identify factors associated with these trajectories, with particular focus on patterns reflecting resilience, recovery, deterioration and persistent impairment. To address the first aim, we apply latent class growth analysis (LCGA) and growth mixture modelling (GMM), methods widely used in psycho-oncology to capture heterogeneity in longitudinal symptom and QoL patterns. To address the second aim, we use logistic regression models to examine associations between candidate predictors and trajectory membership, allowing results to remain clinically interpretable. In addition to univariate analyses, we perform multivariable feature selection using elastic net regularization. Feature selection is used to identify parsimonious sets of predictors that jointly differentiate trajectory groups, while accounting for correlations between variables and limiting overfitting. This approach moves beyond isolated univariate associations and supports clearer interpretation of factors relevant for personalized risk assessment and intervention.

To capture clinically meaningful heterogeneity in longitudinal mental health and quality-of-life (QoL) outcomes, we focus on selected comparisons between trajectory groups that address complementary research questions. Specifically, we examine:

- *Who remains resilient over time*, compared with individuals who experience persistently elevated depressive symptoms or persistently lower QoL, thereby capturing differences in long-term outcome levels.
- *Who is at risk for persistently poor depression or QoL outcomes*, providing insight into profiles associated with sustained vulnerability.
- *Who deteriorates despite early resilience*, a contrast that is less confounded by baseline outcome levels and enables the identification of early warning markers relevant to preventive strategies, clinical monitoring and early intervention.
- *Who recovers among individuals with comparable baseline levels*, a comparison that is likewise less influenced by baseline outcome levels and highlights factors associated with improvement rather than symptom burden, with potential implications for therapeutic intervention.

2. Materials and Methods

2.1. Participants

The BOUNCE project (“Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back”) is a multicenter prospective study designed to identify factors associated with

psychological adaptation following breast cancer diagnosis and treatment (<https://www.bounce-project.eu/>; accessed 20 December 2025). Women diagnosed with breast cancer were recruited from four European countries: Finland (Helsinki University Hospital), Israel (Shaare Zedek Medical Center and Rabin Medical Center, coordinated by the Hebrew University of Jerusalem), Italy (European Institute of Oncology) and Portugal (Champalimaud Clinical Centre). Participants were enrolled approximately three to four weeks from diagnosis.

Eligible participants were female patients aged 40–70 years at diagnosis with histologically confirmed, operable invasive breast cancer (tumor stage I–III), who were receiving surgery as part of local treatment and any form of systemic therapy for breast cancer and who provided written informed consent signed by both the patient and the treating physician. Exclusion criteria included refusal to consent; presence of metastatic disease or a history of another malignancy within the previous five years; a history of severe psychiatric, neurological, (before 40 years of age) or other serious medical conditions; major surgery within the four weeks preceding enrollment; ongoing treatment for another invasive cancer or major illness; and pregnancy or breastfeeding at the time of recruitment. Ethical approval was obtained from the Ethics Committee of the European Institute of Oncology (Approval No. R868/18-IEO916) and from the corresponding ethics committees of all participating centers, while all participants provided written informed consent prior to inclusion.

Data were collected at seven assessment points at three-month intervals, from baseline (M0) to 18 months of follow-up (M18). Psychological symptoms and subjective health status were assessed at all time points, whereas sociodemographic, lifestyle and medical or disease-related variables considered in this analysis were collected at baseline [study protocol at [18]. After applying eligibility criteria and data completeness requirements, the final analytic sample consisted of 538 patients with baseline psychological assessments, at least one long-term follow-up assessment (month 12, 15, or 18) and no more than three missing assessments across the 18-month follow-up period.

2.2. Measures

2.2.1. Outcome Variables

Two outcome variables are considered reflecting psychological distress and health-related quality of life.

Psychological distress was measured using the Depression subscale of the Hospital Anxiety and Depression Scale [19] (HADS). It derives from seven items of the HADS questionnaire, with higher scores (range 0–3 – mean scale) indicating greater severity of depressive symptoms. HADS Depression score was interpreted using established thresholds, with scores of 0–1 indicating low depressive symptoms (corresponding to 0–7 on the 0–21 scale), 1.14–1.42 moderate symptoms (8–10 on the 0–21 scale) and ≥ 1.57 high symptomatology (≥ 11 on the 0–21 scale) [20]. Longitudinal changes were interpreted based on published minimally important difference criteria, whereby changes of approximately 0.2–0.43 points were considered clinically meaningful and changes of ≥ 0.43 points indicative of moderate to large clinical change [21–23].

Overall health-related quality of life was assessed using the Global Health Status/Quality of Life [24] (GHS/QoL) scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). This scale reflects patients' self-reported overall health and quality of life and is derived from two items of the EORTC QLQ-C30, with higher scores (range 0–100) indicating better well-being. As no official clinical cut-offs are defined, interpretation of absolute GHS/QoL levels was guided by published empirical thresholds, with scores ≥ 70 considered indicative of good to excellent quality of life, scores between approximately 50 and 69 reflecting moderate quality of life and scores < 50 indicating poor quality of life [25,26]. Longitudinal changes in GHS/QoL were interpreted using established minimally important difference criteria, with changes of 5–10 points considered small but clinically meaningful and changes ≥ 10 points considered moderate to large [27].

2.2.2. Sociodemographic, Lifestyle and Clinical Data

The analysis incorporated socioeconomic and lifestyle factors, health-related background variables and tumor and treatment characteristics collected at baseline (Table 1).

Table 1. Baseline sociodemographic and lifestyle characteristics of the study participants. Total number of patients n=538.

Variable	Mean (range)	Variable	n (%)
Age	55.4 (40-70)	Monthly Income ¹	
BMI	26 (17.3-54.1)	Low	103 (20.2%)
		Middle	315 (61.6%)
		High	93 (18.2%)
Country/Clinical site		Exercise level ²	
Portugal	134 (24.9%)	None	166 (33.7%)
Italy	95 (17.7%)	Low/moderate	179 (36.4%)
Finland	205 (38.1%)	Heavy	147 (29.9%)
Israel	104 (19.3%)	Diet	
Education		No diet	293 (54.6%)
Non University	211 (39.3%)	Mediterranean/Vegetarian type	166 (30.9%)
University	326 (60.7%)	Special	78 (14.5%)
Marital status		Alcohol behavior ³	
Single/Engaged	53 (9.9%)	No Consumption	107 (22.1%)
Married/Common in Law	400 (74.9%)	Consumption in Moderation	331 (68.2%)
Divorced/Widowed	81 (15.2%)	Heavy Consumption	47 (9.7%)
Employment status		Smoking behavior	
Full/part-time/Self-employed	390 (72.9%)	Current smoker	72 (13.5%)
Unemployed/Housewife	47 (8.8%)	Never smoker	359 (67.4%)
Retired	98 (18.3%)	Former smoker	102 (19.1%)

¹Low monthly income was defined as ≤1,000 EUR for the moderate-income countries (Portugal, Italy) and ≤1,500 EUR for the higher-income countries (Finland, Israel). High monthly income was defined as >3,000 EUR (Portugal, Italy) or >3,500 EUR (Finland, Israel). ²Heavy exercise was defined as ≥200 min/week moderate or ≥100 min/week vigorous aerobic activity and combinations. Moderate aerobic activity includes walking, cycling and similar activities, while vigorous aerobic activity includes running, HIIT training and comparable high-intensity exercises. ³Heavy alcohol consumption was defined as consuming more than 3 drinks on any day or more than 7 drinks per week.

Socioeconomic and lifestyle data collected at baseline included age, body mass index (BMI), ethnicity (Portugal; Italy; Finland; Israel), educational attainment (non-University; University), marital status (single/engaged; married/common-law; divorced/widowed), employment status (employed full-/part-time or self-employed; unemployed/housewife; retired) and monthly household income (low; middle; high). Low monthly income was defined as ≤1,000 EUR in moderate-income countries (Portugal, Italy) and ≤1,500 EUR in higher-income countries (Finland, Israel), whereas high income was defined as >3,000 EUR and >3,500 EUR, respectively.

Lifestyle factors included physical activity level (none; low/moderate; heavy), dietary pattern (no specific diet; Mediterranean/vegetarian-type; special diet), alcohol consumption (no consumption; moderate consumption; heavy consumption) and smoking status (current smoker; never smoker; former smoker). Heavy alcohol consumption was defined as intake of more than three drinks on any day or more than seven drinks per week. Heavy physical activity was defined as ≥ 200 minutes per week of moderate aerobic activity or ≥ 100 minutes per week of vigorous aerobic activity; or ≥ 5 weekly strength-training sessions; or combined aerobic and strength activity meeting ≥ 100 – 180 minutes per week of moderate (or ≥ 50 – 90 minutes per week of vigorous) aerobic exercise with ≥ 1 – 4 weekly strength sessions.

Health history variables included presence of chronic diseases (no/yes), metabolic diseases (no/yes), mental illness (no/yes), exposure to negative life events (none; one event; two or more events) and family history of breast cancer (no/yes). These variables were considered background health factors potentially, treatment tolerance and psychological outcomes.

Clinical and cancer-related data included menopausal status prior to cancer diagnosis (pre-/perimenopausal; postmenopausal), use of hormone replacement therapy before diagnosis (no/yes), tumor stage (I, II, III), tumor grade (I, II, III) and histological subtype (ductal; lobular; other). Tumor biomarker characteristics comprised estrogen receptor (ER) status (negative/positive), progesterone receptor (PR) status (negative/positive), human epidermal growth factor receptor 2 (HER2) status (negative/positive) and Ki67 proliferation index ($< 20\%$; $\geq 20\%$). Molecular subtypes were defined as Luminal A-like (ER+, PR+, HER2-, low Ki67 $< 20\%$); Luminal B-like (HER2-: ER+, PR+/- with high Ki67 $\geq 20\%$ or ER+, PR- with any Ki67; or HER2+: ER+, PR+/- with any Ki67); HER2-positive non-luminal (ER-, PR-, HER2+); and triple-negative (ER-, PR-, HER2-). Treatment-related variables included type of surgery (lumpectomy; mastectomy), receipt of radiotherapy (no/yes), systemic treatment modality (chemotherapy only [\pm anti-HER2 therapy], endocrine therapy only, or combined chemotherapy and endocrine therapy [\pm anti-HER2 therapy]), use of anti-HER2 therapy (no/yes) and administration of neoadjuvant chemotherapy (no/yes).

2.2.3. Psychological Scales

Psychological variables were assessed using validated self-report questionnaires administered at predefined time points throughout follow-up. Relatively stable personality and psychosocial characteristics were assessed at baseline, including optimism using the Life Orientation Test-Revised [28] (LOT-R; 10 items), sense of coherence using the Sense of Coherence Scale [29] (SOC; 13 items assessing meaningfulness, comprehensibility and manageability), trait resilience using the Connor-Davidson Resilience Scale [30] (CD-RISC; 10 items), dispositional mindfulness using the Mindful Attention Awareness Scale [31] (MAAS; 15 items) and general coping capacity using the Perceived Ability to Cope with Trauma Scale [32] (PACT; 20 items). Cancer coping self-efficacy was measured using the brief Cancer Behavior Inventory [33] (CBI-B; 12 items) and Fear of cancer recurrence was also assessed using the Fear of Cancer Recurrence Scale-Short Form [34] (FCR-SF; 9 items), both at baseline. Coping responses to cancer were assessed at three months post-diagnosis using the Mini-Mental Adjustment to Cancer Scale [35] (Mini-MAC; 29 items assessing helplessness-hopelessness, anxious preoccupation, cognitive avoidance and fighting spirit; the fatalism dimension was excluded from analyses). Post-traumatic growth was measured at three months using the Post-Traumatic Growth Inventory-Short Form [36] (PTGI-SF; 10 items).

Anxiety symptoms were assessed every three months using the the Hospital Anxiety and Depression Scale [19] (HADS; 7 items). Emotional functioning was assessed longitudinally every three months using the Positive and Negative Affect Schedule [37] (PANAS; 20 items), while health-related quality of life, including patients' functioning status and symptom burden (e.g., arm symptoms and treatment-related side effects), was assessed every three months using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [24] (EORTC QLQ-C30) and its breast cancer-specific module [24] (EORTC QLQ-BR23).

Several single-item measures were additionally collected to capture specific psychosocial and behavioral aspects. These included a single item assessing what patients reported doing to cope with cancer, a general self-efficacy item and a perceived social support item, all assessed every three months. Adherence to medical advice was assessed using item 5 from the Medical Outcomes Study [38] (MOS) adherence questionnaire.

2.3. Statistical Analysis

2.3.1. Missing Data

Missing data were addressed using multiple imputation by chained equations (mice R package [39]), generating 30 or 50 imputed datasets, depending on the proportion of missingness. All candidate predictors, outcomes and the clinical site variable were included in the imputation models to preserve associations among variables. The random forest-based method was selected.

2.3.2. Derivation of Mental Health and GHS/QoL Trajectories

Latent class growth analysis (LCGA) and growth mixture modelling (GMM) were conducted using the *lcmm* package in R [40] to identify discrete longitudinal trajectories among breast cancer survivors based on EORTC QLQ-C30 GHS/QoL and HADS Depression scores over an 18-month follow-up period. Separate analyses were performed for each outcome. LCGA is a restricted form of GMM in which within-class variances of the random intercept and slope are fixed to zero, allowing heterogeneity only between classes. As random effects are not permitted within classes, LCGA typically requires a larger number of latent classes to adequately capture variability in the data compared with GMM.

To account for non-normal outcome distributions, a six-knot I-spline link function was applied. The choice of link function was informed by preliminary analyses of the null (single-class) model (Appendix A).

Quadratic models of the change across time were considered. For GMM, models with one to six latent classes were estimated, while for LCGA models with one to eight latent classes were considered. Each model was estimated multiple times using a grid of 250 sets of initial values to reduce the risk of convergence to local maxima. For each specified number of latent classes, the model with the highest log-likelihood was retained.

Model selection and determination of the optimal number of latent classes were based on a combination of statistical fit indices, class separation, trajectory shapes, minimum class size, interpretability and clinical relevance [41]. Fit was assessed using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and Integrated Complete Likelihood (ICL), with lower values indicating better fit [41]. Both AIC and BIC balance model fit and complexity, but BIC imposes a stronger, sample-size-dependent penalty and therefore typically selects more parsimonious solutions with fewer latent classes. The ICL further penalizes solutions with poor class separation, jointly accounting for model fit and classification quality. Class separation was further evaluated using entropy and average posterior class membership probabilities, with values greater than 0.60 and 0.70, respectively, indicating adequate separation [42,43]. A minimum class size of at least 5% of the total sample was required.

The *lcmm* framework accommodates missing outcome data, therefore, no imputation of outcome variables was performed.

2.3.3. Determinants of Mental Health and GHS/QoL Trajectories

Once the trajectory groups were identified, binomial logistic regression was conducted to determine which factors at baseline, three-month and six-month follow-up are associated with trajectory group membership.

Initially, associations between individual predictors and the outcome were examined using logistic regression models adjusted for clinical site across imputations. Clinical site was included as

a fixed-effect adjustment variable to account for between-site heterogeneity and results were pooled using Rubin's rules to obtain odds ratios and 95% confidence intervals that reflect uncertainty due to missing data.

Variable selection was conducted using penalized logistic regression with an elastic net penalty, implemented in R using the `glmnet` package [44] (`glmnet` and `cv.glmnet` functions). The elastic net approach was chosen to balance variable selection and coefficient shrinkage while accommodating correlated predictors, which are common in clinical, quality-of-life, and psychosocial data. This strategy supported the identification of robust predictors while maintaining model interpretability and reducing the risk of overfitting. The elastic net mixing parameter was set to $\alpha = 0.5$, providing an equal balance between L1 (LASSO) and L2 (ridge) penalties to achieve stable variable selection in the presence of correlated predictors [45]. Candidate predictors were encoded using model matrices (`model.matrix`), such that categorical variables were represented by indicator variables. The regularization parameter (λ) was selected via 10-fold cross-validation with stratified folds to preserve outcome class proportions within each fold and mitigate the impact of class imbalance. To promote stable and parsimonious models and reduce the risk of overfitting, the one-standard-error rule (λ_{1se}) was used for λ selection [46]. Cross-validation was performed using deviance as the optimization criterion, corresponding to the negative log-likelihood of the logistic model, thereby favoring predictors that improve probabilistic calibration rather than threshold-dependent classification accuracy. The selection procedure was repeated 3 times across all multiple imputed datasets generated using the `mice` package (see 3.3.1) and predictor importance was quantified by selection frequency across imputations and 3 repeats. To evaluate the robustness of our predictors, we conducted the stability analysis under two conditions. Clinical sites were treated as standard predictors subject to the L1/L2 penalty and clinical sites were forced into the model by setting their penalty factor to zero, ensuring their inclusion in every iteration regardless of the regularization threshold. This allowed us to distinguish site-independent predictors from variables reflecting differences in healthcare systems, socioeconomic contexts, and cultural factors. Predictors with high selection frequency (>60%) under both penalized and unpenalized site conditions were considered robust. Descriptive penalized odds ratios were reported to indicate the direction and relative magnitude of associations at the selected regularization parameter under the initial penalized site condition.

Model performance was evaluated using cross-validated predictions from elastic net logistic regression models, with metrics computed on held-out data and averaged across folds, thus reflecting out-of-sample performance. Performance was assessed using ROC-AUC, log-loss, and the Brier score, capturing complementary aspects of predictive quality. ROC-AUC quantifies discrimination, whereas log-loss and the Brier score assess probabilistic accuracy and calibration, with lower values indicating better performance. Although no strict cut-offs exist, ROC-AUC values of 0.60-0.70 indicate poor-to-fair discrimination, 0.70-0.80 acceptable, 0.80-0.90 very good, and >0.90 excellent discrimination [47]; Brier score and log loss were interpreted against chance-level (null-model) values, corresponding to predictions equal to the observed outcome prevalence.

Clinical site was included among candidate predictors during the elastic net selection procedure to assess its stability and potential predictive contribution.

3. Results

3.1. Baseline Demographic and Clinical Characteristics

The study cohort comprised women with a mean age of 55.4 years (40-70) recruited across four countries, most commonly Finland (38.1%), followed by Portugal (24.9%), Israel (19.3%) and Italy (17.7%). The majority had a University education (60.7%), were married or living with a partner (74.9%) and were employed (72.9%), with most reporting middle income levels (61.6%). Regarding lifestyle characteristics, two thirds reported engaging in exercise (66.3%), almost half followed a type

of diet (45.4%), most consumed alcohol in moderation (68.2%) and the majority were never smokers (67.4%).

Clinically, most participants were postmenopausal (61.5%), had stage I–II disease (91.0%), grade II tumors (52.2%) and ductal histology (77.9%). Tumors were predominantly hormone receptor-positive (ER-positive 89.6%; PR-positive 79.8%) and HER2-negative (81.8%), with luminal A-like (36.9%) and luminal B-like HER2-negative (39.0%) subtypes being most frequent. Breast-conserving surgery was the most common surgical approach (74.6%), radiotherapy was administered to 80.6% of patients and systemic treatment most often consisted of endocrine therapy alone (47.3%) or combined chemotherapy and endocrine therapy (37.7%).

Table 2. Baseline clinical and cancer characteristics of the study participants. Total number of patients n=538.

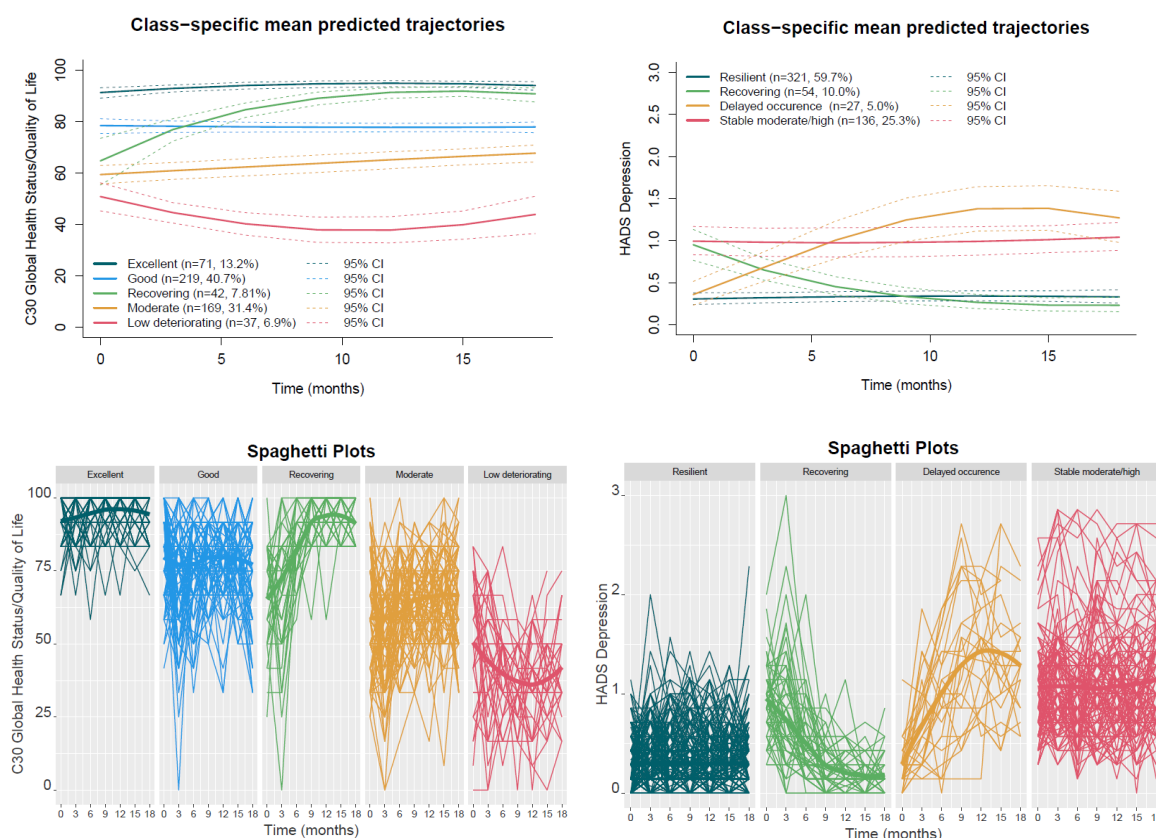
Variable	n (%)	Variable	n (%)
Negative Life Events		Estrogen receptor Positivity	467 (89.6%)
None	58 (12%)	Progesterone receptor Positivity	410 (79.8%)
One event	239 (49.6%)	HER2 Positivity	89 (18.2%)
Two or more events	185 (38.4%)	Ki67 levels $\geq 20\%$	293 (56.7%)
Chronic diseases	191 (35.7%)	Subtypes ¹	
Metabolic diseases		Luminal A-like	175 (36.9%)
Mental illness		Luminal B-like (HER2 -)	185 (39%)
Family history of breast cancer	330 (64.3%)	Luminal B-like (HER2 +)	68 (14.3%)
Menopausal status pre		Her2-positive (non luminal)	20 (4.2%)
Pre/Peri-menopausal	202 (38.5%)	Triple-negative	26 (5.5%)
Postmenopausal	322 (61.5%)	Lumpectomy	391 (74.6%)
HRT before diagnosis	105 (21.6%)	Mastectomy	133 (25.4%)
Cancer stage		Radiotherapy	424 (80.6%)
I	251 (48.2%)	Systemic Therapy	
II	223 (42.8%)	Chemotherapy only (\pm anti-HER2)	78 (14.9%)
III	47 (9%)	Endocrine therapy only	247 (47.3%)
Cancer grade		Chemo + Endocrine therapy (\pm anti-HER2)	197 (37.7%)
I	91 (17.5%)	Anti-HER2 therapy	82 (15.4%)
II	271 (52.2%)	Neoadjuvant Chemotherapy	84 (16%)
III	157 (30.3%)		
Cancer histological type			
Ductal	408 (77.9%)		
Lobular	80 (15.3%)		
Other	36 (6.9%)		

¹Luminal A-like: ER+, PR+, HER2-, low Ki67 (<20%); Luminal B-like (HER2 negative): ER+, PR+/-, HER2-, high Ki67 ($\geq 20\%$) or ER+, PR-, HER2-, Ki67 any; Luminal B-like (HER2 positive): ER+, PR+/-, HER2+, any Ki67; Her2-positive (non luminal) ER-, PR-, HER2+, any Ki67; Triple-negative (ER-, PR-, HER2-, any Ki67) Abbreviations: HRT: Hormone Replacement Therapy; HER2: human epidermal growth factor receptor 2.

3.2. Trajectory Groups

3.2.1. GHS/QoL Trajectories

Taking into account statistical fit, class separation, parsimony and clinical interpretability, we selected the five-class LCGA solution as the optimal model (See Appendix B for detailed explanations). Figure 1a shows the resulting trajectories for the five-group model and the actual measurements of the patients that compose each class. An *Excellent* trajectory (n = 71, 13.2%) demonstrated very high baseline scores (≥ 90) that remained stable throughout the study period. Mean increase in slope is statistically significant (Table D1 in Appendix D) but overall changes are small (< 5 – 10 points), indicating no clinically meaningful change over time, while individual trajectories cluster tightly at high values with limited variability. The largest class was the *Good* trajectory (n = 219, 40.7%), characterized by consistently high QoL scores primarily within the good range (≥ 70). The mean trajectory was essentially flat (Table D1 in Appendix D). This class exhibited greater individual variability than the Excellent class; however, most observations remained ≥ 70 throughout follow-up. The *Moderate* class (n = 169, 31.4%) exhibited baseline and follow-up scores predominantly within the moderate range (50–69). Substantial within-class variability was observed, with some individuals showing improvement over time while others remained stable or fluctuated across follow-up. Overall, the mean trajectory remained largely stable (Table D1 in Appendix D). A small *Recovering* class (n = 42, 7.8%) started with moderately reduced QoL (approximately 60–65) but exhibited a marked and sustained improvement exceeding clinically important change thresholds (≥ 10 points), reaching levels comparable to the higher-functioning classes by the end of follow-up. Most individuals in this class showed upward trajectories crossing the threshold for clinical importance. Finally, the *Low deteriorating* class (n = 37, 6.9%) showed low baseline QoL near or below the poor range (< 50), with further statistically important (Table D1 in Appendix D) and clinically meaningful deterioration during the early months followed by only partial recovery. The early decline exceeded 10 points, representing clinically meaningful deterioration and subsequent improvement did not fully offset this loss. Although within-class variability was high, most individuals remained below 50–55 for much of the follow-up period.



(a) (b)

Figure 1. Mean growth trajectories and observed individual patient trajectories, grouped by trajectory latent classes for (a) EORTC QLQ-C30 Global Health Status/Quality of Life scores and (b) HADS Depression scores.

3.2.2. HADS Depression Trajectories

We selected the four-class GMM solution as the optimal model (See Appendix C for detailed explanations). Figure 1b shows the resulting trajectories for the four-group model and the actual measurements of the patients that compose each class. The largest group was the *Resilient* trajectory ($n = 321$, 59.7%), characterized by persistently very low depressive symptom levels throughout follow-up. Within this class, variability was minimal, with overall or individual mean changes being negligible or very small (Table D2 in Appendix D). The *Stable moderate/high* trajectory ($n = 136$, 25.3%) exhibited consistently elevated depressive symptoms (mild to moderate range) that remained largely stable over time (Table D2 in Appendix D), indicating a chronic symptom burden. For most patients in this class, depressive symptom scores fluctuated considerably from one assessment to another (>0.2), yet the overall individual trajectories remained stable over time. A smaller *Recovering* trajectory ($n = 54$, 10.0%) showed higher baseline depressive symptoms followed by a sustained and clinically meaningful decrease over time (Table D2 in Appendix D), with most individuals improving to very low symptom levels (<0.4). Finally, the *Delayed occurrence* trajectory ($n = 27$, 5.0%) demonstrated low baseline depressive symptoms with a gradual, statistically significant (Table D2 in Appendix D) and clinically meaningful increase during follow-up, reaching levels >1 , indicative of delayed onset of depressive symptomatology.

3.3. Predictors of C30 GHS/QoL Trajectories

3.3.1. Low Deteriorating QoL vs Rest

In clinical-site-adjusted univariable logistic regression analyses (Supplementary Figure S1), higher odds of membership in the low deteriorating QoL class were observed among unemployed/housewives (OR 2.49), individuals with ≥ 2 negative life events (OR 5.30), those with chronic disease (OR 1.80) or mental illness (OR 4.92), higher BMI (OR 1.08 per unit), adverse tumor characteristics including stage III disease (OR 2.99), grade III tumors (OR 3.74), Ki-67 $\geq 20\%$ (OR 2.20), triple-negative subtype (OR 3.51), and receipt of neoadjuvant chemotherapy (OR 4.45). In contrast, middle income (OR 0.35), physical activity (low/moderate: OR 0.22; heavy: OR 0.10), moderate alcohol consumption (OR 0.42), estrogen receptor positivity (OR 0.29), endocrine therapy alone (OR 0.23), and combined chemo-endocrine therapy (OR 0.32) were associated with lower odds.

Both at baseline and month 3, the vast majority of considered psychological, psychosocial, and health-related quality-of-life scales differed significantly between patients in the low deteriorating QoL class and all other classes (Supplementary Figures S2, S3).

Baseline psychological distress was strongly associated with higher odds, including depression (HADS; OR 6.19), anxiety (HADS; OR 3.87), fear of cancer recurrence (FCRI; OR 2.60), distress (NCCN; OR 1.24), and negative affect (PANAS; OR 2.41), other blame (CERQ; OR 2.53), catastrophizing (CERQ; OR 1.45), overall negative cognitive emotion regulation score (CERQ; OR 2.76), whereas optimism (OR 0.39), sense of coherence (ORs 0.82–0.89), acceptance (CERQ; OR 0.77) ability to cope with trauma (trauma-focus, forward-focus, flexibility, total PACT; ORs 0.60–0.78), mindfulness (MAAS; OR 0.48), resilience (CDRISC; OR 0.43), coping with cancer (CBI; OR 0.53), self-efficacy (OR 0.73), perceived social support (OR 0.69), and positive affect (PANAS; OR 0.45), put into perspective (CERQ; OR 0.62) were protective. Similarly, better baseline global health status/QoL (C30; OR 0.94), and functioning across almost all domains (physical, role, social, emotional and cognitive C30; ORs 0.95–0.98) were associated with lower odds, while higher financial impact (C30; OR 1.02) and symptom burden (fatigue, pain, arm symptoms, dyspnea, insomnia, appetite loss, constipation, diarrhea and systemic therapy side effects C30 or BR23; ORs 1.01–1.05) were associated with higher

odds. Moreover, better body image (BR23; OR 0.98), future perspective (BR23; OR 0.99), and sexual enjoyment (BR23; OR 0.99) were associated with lower odds.

The scales not significantly associated with membership in the low deteriorating QoL class were: polarity (PACT), most CERQ scales (self-blame, rumination, positive refocusing, positive reappraisal and planning; although there is a tendency to significance with the exception of planning and self-blame), as well as nausea (C30), breast symptoms (BR23), sexual function (BR23) and upset by hair loss (BR23).

At month 3, patients in the low deteriorating QoL class showed substantially higher psychological distress compared with all other patients, including depression (HADS; OR 6.97), anxiety (HADS; OR 5.93), distress (NCCN; OR 1.29) negative affect (PANAS; OR 2.44), anxious preoccupation (MAC; OR 3.54) and helplessness (MAC; OR 3.92). Conversely, positive affect (PANAS; OR 0.37), perceived social support (OR 0.78), general self-efficacy (OR 0.71), adaptive family communication and cohesion (FARE; ORs 0.56–0.58), personal control beliefs (OR 0.85), and positive treatment beliefs (OR 0.67) were associated with lower odds. Among coping behaviors, exercising (OR 0.62) and looking at positive aspects (OR 0.76) were protective.

Health-related QoL at month 3 similarly differentiated trajectories. Better global health status/QoL (OR 0.95) and higher functioning (physical, role, emotional, cognitive, and social functioning C30; ORs 0.94–0.97) were associated with lower odds of low deteriorating QoL, whereas greater C30 symptom burden—including fatigue (OR 1.04), pain (OR 1.03), dyspnea (OR 1.03), insomnia (OR 1.02), appetite loss (OR 1.02), diarrhea (OR 1.02), financial impact (OR 1.02), and treatment-related side effects (OR 1.05)—was associated with higher odds. Breast cancer-specific domains further characterized this group, including poorer body image (OR 0.98), more breast and arm symptoms (ORs 1.03), reduced future perspective (OR 0.98), and lower sexual functioning and enjoyment (ORs 0.97–0.98).

Variables related to post-traumatic growth (PTGI; relating to others, new possibilities, personal strength, spiritual change, appreciation of life, total score), mental adjustment styles (MAC; fighting spirit, avoidance, fatalism,) and certain copying behaviors (tried to relax, distracted yourself, prayed, etc.) showed no statistically significant difference between the groups.

To identify robust features associated with the low deteriorating QoL profile, we implemented a feature selection pipeline based on elastic net logistic regression across 30 multiply imputed datasets under penalized site and unpenalized site conditions. Predictor importance was quantified using selection frequency. Predictive model performance was evaluated using cross-validated predictions from elastic net logistic regression models.

A limited set of features emerged as robust in distinguishing the low-deteriorating class from the remaining patients (Table 3). At baseline, depressive symptoms, emotional functioning, global health status/quality of life (GHS/QoL), fatigue, pain, diarrhea, sense of manageability, coping with cancer, perceived social support, and other-blame coping were the most stable predictors, each selected with 100% or near-100% ($\geq 97\%$) frequency under both penalized and unpenalized clinical site conditions. Receipt of neoadjuvant chemotherapy and triple-negative molecular profile followed, also demonstrating high selection stability. Negative life events showed borderline selection frequency, suggesting a weaker and less consistent contribution to the model.

At month 3, cognitive functioning, depressive symptoms, physical functioning, and treatment control beliefs emerged as the most robust predictors, each being selected in 100% of the 90 stability iterations under both penalized and unpenalized clinical site conditions. These were followed by anxiety symptoms and family communication and cohesion. In contrast, neoadjuvant chemotherapy showed unstable selection when the clinical site was forced into the model.

Both at baseline and month 3, the models demonstrated strong discriminative ability (ROC-AUC ~ 0.86) and high probabilistic accuracy (for chance performance $\log\text{-loss}=0.253$ and Brier score=0.064) (Table 3).

Table 3. Stability-selected predictors distinguishing the low deteriorating QoL trajectory from all other trajectory classes with descriptive penalized odds ratios.

Variable	Selection Freq (%)		Mean OR ¹ Penalized Site
	Penalized Site	Unpenalized Site	
Baseline			
Performance²: log-loss = 0.191, Brier score = 0.052, ROC-AUC = 0.855			
Depression HADS	100%		1.4081
Diarrhea C30	100%		1.004
Emotional functioning C30	100%		0.9976
Fatigue C30	100%		1.0011
GHS/QoL C30	100%		0.9857
Coping with cancer CBI	100%		0.9623
Manageability SOC	100%		0.9548
Other blame CERQ	100%		1.2173
Pain C30	100%		1.0154
Neoadjuvant Chemotherapy	100%		1.4209
Perceived support 1 item	100%		0.8896
Triple-negative	83%		1.429
Negative Life Events: Two or more (ref. No)	67%		1.0899
Month 3³			
Performance²: log-loss = 0.196, Brier score = 0.0537, ROC-AUC = 0.855			
Cognitive Function C30	100%		0.9924
Depression HADS	100%		1.8171
Physical Function C30	100%		0.9875
Treatment control beliefs	100%		0.9005
Anxiety HADS	90%		1.1226
Neoadjuvant Chemotherapy	73%		1.1347
Communication and cohesion FARE	70%		0.9455

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ GHS/QoL C30 was not included in the variables at month 3.

3.3.2. Excellent QoL vs Rest

Compared with all other classes (Supplementary Figure S4), excellent QoL was associated with older age (OR 1.03), heavy physical activity (OR 2.60), moderate alcohol consumption (OR 2.24), lower BMI (OR 0.93), no negative life events (ORs 0.36–0.17), and absence of mental illness (OR 0.09). Favorable disease characteristics, including lower stage (ORs 0.58–0.20), lower grade (ORs 0.50–0.34), low Ki-67 (OR 0.53) and luminal A-like subtype (OR 2.13), were also associated with excellent QoL. In contrast, neoadjuvant chemotherapy was inversely associated (OR 0.15), whereas endocrine therapy alone was positively associated (OR 2.67) with excellent QoL.

At baseline and month 3, almost all considered psychological, psychosocial, and health-related quality-of-life scales differed significantly between patients in the excellent QoL class and all other classes, with consistent advantages observed across distress, coping, affect, functioning, and symptom domains (Supplementary Figures S5-S6).

At baseline, the Excellent QoL group was less likely to report negative psychological traits, including depressive symptoms (HADS; OR = 0.06), anxiety (HADS; OR = 0.14), fear of recurrence

(FCRI; OR = 0.42), self-blame (CERQ; OR = 0.53), other-blame (CERQ; OR = 0.59), catastrophizing (CERQ; OR = 0.38), and overall negative cognitive emotion regulation strategies (CERQ; OR = 0.29).

Conversely, the Excellent QoL group was more likely to report positive psychological traits, including optimism (LOT; OR = 2.36); comprehensibility (SOC; OR = 1.16), manageability (SOC; OR = 1.15), and meaningfulness (SOC; OR = 1.18); positive coping strategies (PACT: forward focus OR = 1.56, trauma focus OR = 1.72, total coping OR = 1.36); adaptive emotion regulation strategies (CERQ: perspective-taking OR = 1.43, positive refocusing OR = 1.57, positive reappraisal OR = 1.37, acceptance OR = 1.41); mindfulness (MAAS; OR = 2.65); resilience (CDRISC; OR = 3.89); and positive affect (PANAS; OR = 2.97).

Moreover, better baseline global health status/QoL (C30; OR = 1.14) and better functioning across all C30 domains, including physical (OR = 1.09), role (OR = 1.05), emotional (OR = 1.07), cognitive (OR = 1.06), and social functioning (OR = 1.05), were associated with higher odds of belonging to the Excellent QoL class. In contrast, greater symptom burden, including fatigue (OR = 0.95), nausea (OR = 0.92), pain (OR = 0.95), dyspnea (OR = 0.97), insomnia (OR = 0.98), appetite loss (OR = 0.97), constipation (OR = 0.97), and diarrhea (OR = 0.96) (C30), as well as systemic therapy side effects (BR23; OR = 0.92), breast symptoms (OR = 0.98), and arm symptoms (OR = 0.96), was associated with lower odds of Excellent QoL. Moreover, better body image (BR23; OR = 1.04), future perspective (BR23; OR = 1.03), sexual function (BR23; OR = 1.01), and sexual enjoyment (BR23; OR = 1.01) were associated with higher odds of Excellent QoL.

Rumination (CERQ), planning (CERQ), polarity (PACT) and upset hair image (BR23) did not show a statistically significant difference between the two groups.

At month 3, individuals in the Excellent QoL group showed significant differences across a wide range of psychosocial and coping variables. They were significantly more likely to report strong family communication and cohesion (FARE; OR = 2.43), effective family coping (FARE; OR = 2.17), higher general self-efficacy (single item; OR = 1.76), better adherence to medical advice (OR = 1.56), greater perceived social support (single item; OR = 1.52), instrumental support (mMOS; OR = 1.53), emotional support (mMOS; OR = 2.12), and overall social support (mMOS; OR = 2.01). They also reported higher positive affect (PANAS; OR = 5.46), stronger personal control beliefs (OR = 1.28), treatment control beliefs (OR = 1.36), and greater use of exercise as a coping behaviour (OR = 1.34).

Conversely, the Excellent QoL group was significantly less likely to report depressive symptoms (HADS; OR = 0.03), anxiety (HADS; OR = 0.07), overall mental health distress (HADS total; OR = 0.02), general distress (NCCN Distress Thermometer; OR = 0.62), helplessness (MAC; OR = 0.15), anxious preoccupation (MAC; OR = 0.21), avoidance coping (MAC; OR = 0.56), negative affect (PANAS; OR = 0.15), and the coping behaviors crying (OR = 0.47), talking to the physician (OR = 0.62) or ask for help (OR 0.79).

All health-related QoL domains at Month 3 differentiated between trajectory groups. Better global health status/QoL and higher overall functioning were associated with a greater likelihood of belonging to the Excellent QoL class (ORs 1.05–1.16), whereas greater symptom burden and financial impact were associated with lower odds (ORs 0.93–0.98). Breast cancer-specific domains further contributed to this differentiation, with better body image, future perspective, and sexual functioning (ORs 1.01–1.04) and fewer treatment-related, breast, and arm symptoms (ORs 0.94–0.98) characterizing the Excellent QoL group.

Variables related to post-traumatic growth (PTGI; relating to others, new possibilities, personal strength, spiritual change, appreciation of life, and total PTGI score), specific mental adjustment styles (MAC; fighting spirit and fatalism), and certain coping behaviors (e.g., trying to relax, distraction, praying, and looking at positive sides and perceiving the situation as a challenge) showed no statistically significant differences between the groups.

Stability selection at baseline and month 3 identified a relatively broad set of factors distinguishing the excellent QoL class (Table 4).

At baseline, robust predictors were associated with psychological resources and lower distress, including lower anxiety and higher mindfulness, resilience, coping, self-efficacy, and perceived social

support. Better global health status and functioning across physical, role, emotional, and cognitive domains, together with lower catastrophizing and symptom burden, further differentiated the excellent QoL class. In addition, treatment-related factors (receipt of endocrine therapy and absence of neoadjuvant chemotherapy), favorable molecular phenotypes (more Luminal A-like and less Luminal B-like [HER2+]), and selected sociodemographic characteristics (not being unemployed/housewife or following a vegetarian diet) contributed to class differentiation. Notably, the stability of pre-existing mental illness and positive affect dropped well below 60% when clinical site was forced into the model.

At month 3, robust predictors reflected lower psychological distress and treatment-related symptom impact, including lower anxiety, anxious preoccupation, fatigue, systemic therapy side effects, and distress, alongside greater positive affect, future perspective, and role and social functioning. These variables were selected in 100% or near-100% of stability iterations. Additional contributors included better physical and emotional functioning, stronger personal control beliefs, greater perceived social and emotional support, lower pain and arm symptoms, fewer depressive symptoms, better family communication and cohesion, and reduced exposure to multiple negative life events. In contrast, the stability of negative affect declined markedly when clinical site effects were accounted for.

Both at baseline and month 3, the models demonstrated strong discriminative ability and high probabilistic accuracy (for chance performance log-loss=0.390 and Brier score=0.115) (Table 4).

Table 4. Stability-selected predictors distinguishing the excellent QoL trajectory (reference) from all other trajectory classes, with descriptive penalized odds ratios.

Variable	Selection Freq (%)	Mean OR ¹	Selection Freq (%)
	Penalized Site	Penalized Site	Unpenalized Site
Baseline			
Performance²: log-loss = 0.276, Brier score = 0.0852, ROC-AUC = 0.879			
Anxiety HADS	100%	0.8796	93%
Cognitive functioning C30	100%	1.0059	100%
Constipation C30	100%	0.998	100%
Emotional functioning C30	100%	1.0068	100%
Mental illness (ref. No)	100%	0.8947	10%
Fatigue C30	100%	0.9955	100%
GHS/QoL C30	100%	1.0501	100%
Mindfulness MAAS	100%	1.224	100%
Resilience CDRISC	100%	1.2044	100%
Self blame CERQ	100%	0.8493	100%
Physical functioning C30	100%	1.0106	100%
Role functioning	100%	1.0029	100%
Luminal A-like	100%	1.3491	100%
Israel (ref.Portugal)	100%	1.1341	-
Endocrine only (ref. Chemo only +/-Anti-HER2)	100%	1.107	63%
Mediterranean/Vegetarian diet (ref. None)	100%	0.9513	70%
Unemployed/Housewife (ref. Full-time/Self-employed)	100%	0.9384	100%
Neoadjuvant Chemotherapy	100%	0.7816	100%
Perceived support 1 item	100%	1.0287	97%
Future Perspective Image BR23	97%	1.0014	97%
Meaningfulness SOC	93%	1.0026	80%
Positive affect PANAS	93%	1.014	0%

General self-efficacy 1 item	93%	1.0907	90%
Arm Symptoms BR23	90%	0.9991	100%
Distress thermometer NCCN	90%	0.9624	90%
Coping with cancer CBI	87%	1.0278	100%
Luminal B-like (HER2 +)	83%	0.9583	63%
Catastrophizing CERQ	80%	0.9764	97%
Negative Life Events: Two or more (ref. No)	77%	0.9199	77%
Month 3³			
Performance²: log-loss = 0.306, Brier score = 0.0928, ROC-AUC = 0.845			
Anxiety HADS	100%	0.744	100%
Fatigue C30	100%	0.988	100%
Anxious preoccupation MAC	100%	0.8719	100%
Positive affect PANAS	100%	1.3538	100%
Role functioning	100%	1.0055	100%
Systemic Therapy Side Effects BR23	100%	0.9963	100%
Social functioning	100%	1.004	100%
Personal control beliefs over illness	100%	1.0147	80%
Distress thermometer NCCN	100%	0.9693	97%
What done to cope: Talked to the physician	100%	0.9495	97%
Future Perspective Image BR23	97%	1.0027	97%
Depression HADS	93%	0.8901	80%
Negative affect PANAS	93%	0.9418	13%
Physical functioning C30	93%	1.003	97%
Perceived support 1 item	93%	1.0361	90%
Arm Symptoms BR23	90%	0.9974	90%
Emotional functioning C30	83%	1.003	87%
Communication and cohesion FARE	77%	1.0215	83%
Pain C30	77%	0.9962	83%
Emotional support mMOS	73%	1.0395	67%
Negative Life Events: Two or more (ref. No)	70%	0.916	83%

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ GHS/QoL C30 was not included in the variables at month 3.

3.3.3. Recovery vs Moderate QoL

Among sociodemographic, lifestyle, clinical, and cancer-related factors, clinical-site-adjusted univariable logistic regression analyses (Supplementary Figure S7) identified exposure to negative life events as the only factor significantly associated with QoL recovery, with lower odds observed across increasing exposure levels (OR range = 0.16–0.29).

Several baseline (M0) factors were significantly associated with QoL recovery. Protective factors included higher optimism (LOT; OR = 2.72), greater resilience (CD-RISC; OR = 2.42), greater coping flexibility (PACT; OR range = 1.23–1.52), and greater use of adaptive cognitive emotion regulation strategies, such as perspective-taking (CERQ; OR = 1.57) and planning (CERQ; OR = 1.72), all of which were associated with increased odds of recovery. In contrast, risk factors included higher depressive symptoms (HADS; OR = 0.40), anxiety symptoms (HADS; OR = 0.46), and greater use of catastrophizing (CERQ; OR = 0.63), which were associated with lower odds of QoL recovery (Supplementary Figure S8). Regarding health-related QoL domains at Month 3, better global health

status/QoL (C30; OR = 1.03) and higher functioning, including physical (OR = 1.03), role (OR = 1.02), emotional (OR = 1.02), and social functioning (all C30; OR = 1.03), were associated with a greater likelihood of belonging to the *Recovery QoL* class. In contrast, higher symptom burden, particularly fatigue (C30; OR = 0.97) and pain (C30; OR = 0.97), was associated with lower odds of recovery. Among breast cancer-specific domains, better sexual functioning (EORTC QLQ-BR23; OR = 1.02) was positively associated with QoL recovery, whereas most symptom and body image domains did not significantly differentiate recovery trajectories.

The psychological scales not significantly associated with membership in the *Recovery QoL* class included sense of comprehensibility, manageability, and meaningfulness (SOC); fear of recurrence (FCRI); trauma and total coping (PACT), with polarity coping showing only a borderline association; most cognitive emotion regulation strategies (CERQ), including self-blame, other-blame, rumination, positive reappraisal, acceptance, and negative overall CERQ (with borderline effects for positive refocusing and acceptance); distress (NCCN Distress Thermometer); and negative affect (PANAS).

At Month 3, site-adjusted models indicated that lower symptom burden and more adaptive coping remained associated with QoL recovery. Specifically, lower helplessness (MAC; OR = 0.13), lower anxious preoccupation (MAC; OR = 0.34), lower anxiety and depressive symptoms (HADS; ORs=0.12-0.21), lower distress (NCCN; OR = 0.86), lower negative affect (PANAS; OR=0.52), higher fighting spirit (MAC; OR = 3.93), higher positive affect (PANAS; OR = 3.46), greater general self-efficacy (OR = 1.74), stronger personal and treatment control beliefs (ORs = 1.39–1.78), higher family coping (FARE; OR=1.82) and greater emotional support (mMOS; OR = 2.01) were significant predictors of recovery. In addition, better global health status/QoL and higher functioning (physical, role, emotional, cognitive, and social; C30; ORs = 1.02–1.05), lower pain (C30; OR = 0.97), fatigue and nausea (C30; ORs = 0.97–0.98), and better sexual functioning, enjoyment, and future perspective (BR23; ORs = 1.02–1.03) were also associated with increased odds of QoL improvement (Supplementary Figure S9).

At Month 3, the scales that did not differ between the groups were post-traumatic growth (PTGI; relating to others, new possibilities, personal strength, spiritual change, appreciation of life, and total PTGI score), mental adjustment styles reflecting avoidance and fatalism (MAC), family communication and cohesion (FARE), adherence to medical advice, several coping behaviors (including trying to relax, distraction, praying/going to church, exercising, bursting into tears, talking to or asking help from someone important, and talking to the physician), and instrumental social support (mMOS). In terms of health-related QoL, dyspnea, insomnia, constipation, diarrhea, and financial impact (EORTC QLQ-C30), as well as breast symptoms, arm symptoms, and upset by hair loss (EORTC QLQ-BR23), did not significantly differ between groups.

A concise set of features emerged as robust in distinguishing the recovery class from the moderate QoL one (Table 5). At baseline, coping with cancer, mindfulness, optimism, perspective-taking emotion regulation, pain, positive affect, sexual functioning, and social functioning, together with middle and high income (vs low income), emerged as the most robust predictors, had a selection frequency of 100% or above 90%. These were followed by planning as a cognitive emotion regulation strategy. The stability of resilience, exposure to two or more negative life events, adherence to a special diet dropped markedly when clinical site was forced into the model. No psychological distress symptoms emerged as robust predictors.

At month 3, a similarly concise set of features robustly distinguished the recovery QoL class from the rest of the patients (Table 5). Helplessness, pain, positive affect, sexual functioning, personal control beliefs over illness, middle and high income (vs low income), coping by perceiving the situation as a challenge and general self-efficacy were the most stable predictors, each selected in 100% or nearly 100% of the stability iterations, even when clinical site was forced in the model. These were followed by social functioning, fighting spirit, depression and anxiety symptoms. The selection frequency of postmenopausal status, negative life events and and triple-negative disease dropped below the threshold when clinical site was forced into the model.

At baseline, the model showed fair discrimination and moderate probabilistic accuracy (Table 5; for chance performance log-loss=0.500 and Brier score=0.159). At month 3, performance improved, with good discrimination and better calibration and accuracy, indicating enhanced predictive ability over time. Together, these results suggest that incorporating baseline and month 3 information would substantially enhance the model's ability to predict QoL trajectories compared with baseline alone.

Table 5. Stability-selected predictors distinguishing the moderate QoL trajectory from the recovering QoL trajectory (reference), with descriptive penalized odds ratios.

Variable	Selection Freq (%)	Mean OR ¹	Selection Freq (%)
	Penalized Site	Penalized Site	Unpenalized Site
Baseline			
Performance²: log-loss = 0.464, Brier score = 0.147, ROC-AUC = 0.681			
Coping with cancer CBI	100%	1.0568	97%
Mindfulness MAAS	100%	1.0276	93%
Optimism LOT	100%	1.1892	100%
Perspective CERQ	100%	1.0756	90%
Resilience CDRISC	100%	1.0604	0%
Pain C30	100%	0.9978	100%
Positive affect PANAS	100%	1.0919	100%
Sexual functioning BR23	100%	1.0033	90%
Social functioning C30	100%	1.0047	100%
Income Middle (ref. Low)	100%	0.7621	97%
Income High (ref. Low)	100%	1.5861	100%
Postmenopausal	93%	1.0937	17%
Planning CERQ	90%	1.0193	70%
Negative Life Events: Two or more (ref. No)	80%	0.9259	77%
Special diet (ref. None)	63%	0.9428	37%
Month 3³			
Performance²: log-loss = 0.432, Brier score = 0.136, ROC-AUC = 0.763			
Helpless MAC	100%	0.7512	100%
Pain C30	100%	0.9945	100%
Positive affect PANAS	100%	1.1766	100%
Sexual functioning BR23	100%	1.0065	100%
Non Luminal (HER2 +)	100%	1.3504	60%
Personal control beliefs over illness	100%	1.0572	100%
Income Middle (ref. Low)	100%	0.7705	100%
Income High (ref. Low)	100%	1.6132	100%
Postmenopausal	100%	1.1308	7%
What done to cope: See it as a challenge	100%	1.1008	100%
General self-efficacy 1 item	97%	1.0398	97%
Triple negative	93%	0.8909	33%
Social functioning	87%	1.0019	97%
Fighting MAC	80%	1.1059	73%
Depression HADS	77%	0.9431	83%
Anxiety HADS	70%	0.9368	83%
Negative Life Events: Two or more (ref. No)	70%	0.9331	53%

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ GHS/QoL C30 was not included in the variables at month 3.

3.4. Predictors of HADS Depression Trajectories

3.4.1. Stable Moderate/High vs Resilient

Compared with the *Resilient* class, several protective factors were associated with lower odds of belonging to the *Stable Moderate/High Depression* class, including residence in Finland (vs Portugal) (OR = 0.43), university education (OR = 0.52), being married or in a common-law relationship (vs. single) (OR = 0.47), higher income (OR = 0.38), postmenopausal status (OR = 0.59), engagement in physical activity (heavy: OR = 0.32), and moderate alcohol consumption (OR = 0.49). In contrast, risk factors associated with higher odds of stable moderate/high depression included residence in Italy (vs Portugal) (OR = 3.56), unemployment or being a housewife (OR = 2.59), exposure to two or more negative life events (OR = 2.38), history of mental illness (OR = 3.99), HER2-positive (non-luminal) tumor subtype (OR = 3.59), and receipt of neoadjuvant chemotherapy (OR = 2.20) (Supplementary Figure S10).

At baseline, the scales that did not show statistically significant differences between the Resilient and Stable Moderate/High Depression groups were self-blame (CERQ) and acceptance (CERQ), with other-blame (CERQ) showing only a borderline association. All other psychological, coping, and affective scales, as well as all health-related quality-of-life domains were significantly associated with group membership (Supplementary Figure S11).

At Month 3, the scales not significantly associated with group membership between the Resilient and Stable Moderate/High Depression classes were post-traumatic growth dimensions (PTGI; relating to others, new possibilities, personal strength, appreciation of life, and total PTGI score), with the exception of spiritual change, fatalism (MAC), and few coping behaviors (trying to relax, praying/going to church, talking to or asking for help from somebody important). In terms of health-related QoL, only diarrhea (C30) did not significantly differ between the groups. All other psychological, coping, social support, and QoL scales demonstrated statistically significant associations (Supplementary Figure S12).

The feature selection procedure identified a concise set of variables that robustly distinguished the stable moderate/high depression class from the resilient class (Table 6). At baseline, risk factors consistently selected across all stability iterations included higher anxiety and depressive symptoms, greater arm symptoms, higher financial impact, poorer future perspective, greater catastrophizing, lower sense of manageability and meaningfulness, lower optimism, poorer role functioning, and residence in Italy or Finland (vs Portugal). Additional variables distinguishing the stable moderate/high class were higher distress and lower resilience. Stability of coping with cancer, heavy exercise (vs none), unemployment or being a housewife (vs employment) dropped to 0% when clinical site was forced into the model.

At month 3, variables consistently selected across all stability iterations and penalized clinical site conditions included anxiety, distress, anxious preoccupation, negative affect, helplessness, emotional functioning, positive affect, greater emotional support and residence in Italy or Finland (vs Portugal). Additional selected variables included fatigue, pain, arm symptoms, spiritual change, sexual functioning and enjoyment and cognitive functioning. In contrast, the selection frequency of avoidance coping, radiotherapy, university education, use of exercise as a coping strategy and heavy physical activity dropped considerably, even to 0 when clinical site was forced to the model.

At baseline, the model demonstrated excellent discrimination and calibration performance, while at month 3, performance remained high, though slightly reduced, indicating robust predictive ability at both time points (Table 6; for chance performance log-loss=0.610 and Brier score=0.209).

Table 6. Stability-selected predictors distinguishing the stable moderate/high depression trajectory class (reference) from the resilient class, with descriptive penalized odds ratios.

Variable	Selection Freq (%)	Mean OR ¹	Selection Freq (%)
	Penalized Site	Penalized Site	Unpenalized Site
Baseline			
Performance²: log-loss = 0.300, Brier score = 0.0892, ROC-AUC = 0.941			
Anxiety HADS	100%	1.2873	100%
Arm Symptoms BR23	100%	1.0028	100%
Depression HADS	100%	15.3494	100%
Financial impact C30	100%	1.0006	100%
Future Perspective Image BR23	100%	0.9978	100%
Catastrophizing CERQ	100%	1.1142	100%
Manageability SOC	100%	0.9752	100%
Meaningfulness SOC	100%	0.9872	100%
Optimism LOT	100%	0.9384	100%
Resilience CDRISC	100%	0.7783	63%
Role functioning	100%	0.9948	100%
Italy (ref.Portugal)	100%	1.3646	-
Finland (ref.Portugal)	100%	0.8601	-
Unemployed/Housewife (ref. Full/part-time/Self-employed)	100%	1.2159	0%
Coping with cancer CBI	93%	0.9806	0%
Distress thermometer NCCN	90%	1.0306	77%
Exercise level: Heavy (ref. No)	80%	0.937	0%
Month 3³			
Performance²: log-loss = 0.370, Brier score = 0.115, ROC-AUC = 0.905			
Anxiety HADS	100%	1.8654	100%
Emotional functioning C30	100%	0.9941	100%
Future Perspective Image BR23	100%	0.9949	100%
Anxious preoccupation MAC	100%	1.3574	100%
Helpless MAC	100%	1.3366	100%
Spiritual change PTGI	100%	1.0459	73%
Emotional support mMOS	100%	0.7919	100%
Negative affect PANAS	100%	1.5575	100%
Positive affect PANAS	100%	0.8326	100%
Italy (ref.Portugal)	100%	1.7245	-
Finland (ref.Portugal)	100%	0.709	-
Exercise level: Heavy (ref. No)	100%	0.828	20%
Distress thermometer NCCN	100%	1.0686	100%
Radiotherapy	100%	0.9329	0%
Fatigue C30	97%	1.0028	97%
Pain C30	97%	1.0027	90%
Sexual Enjoyment BR23	93%	0.997	77%
Arm Symptoms BR23	90%	1.0023	80%
Sexual functioning BR23	83%	0.9974	80%
University education	80%	0.9706	0%
What done to cope: Exercised	80%	0.9772	17%
Cognitive Function C30	70%	0.9986	93%
Avoidance MAC	63%	1.0353	0%

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ Depression HADS was not included in the variables at month 3.

3.4.2. Delayed occurrence vs Resilient

Regarding sociodemographic, lifestyle and clinical data, compared with the *Resilient* class, several risk factors were associated with a higher likelihood of belonging to the *Delayed Occurrence Depression* class. These included history of mental illness (OR = 42.84), HER2-positive tumors (OR = 2.99), triple-negative breast cancer subtype (OR = 3.63), and receipt of anti-HER2 therapy (OR = 2.91). Additional risk was observed for individuals with HER2-positive (non-luminal) tumors (OR = 4.80). In contrast, several protective factors were associated with lower odds of delayed depression, including residence in Finland (vs Portugal) (OR = 0.15), university education (OR = 0.28), middle and high income (vs low income) (ORs = 0.22–0.25), engagement in physical activity (low–moderate: OR = 0.32; heavy: OR = 0.20), never or former smoking (ORs = 0.21–0.31), and estrogen receptor-positive disease (OR = 0.29).

At baseline, poorer psychological resources and quality of life were significantly associated with higher odds of belonging to the *Delayed Occurrence Depression* class. Specifically, lower optimism (LOT; OR = 0.34), lower sense of coherence, including manageability (SOC; OR = 0.86) and meaningfulness (SOC; OR = 0.85), lower resilience (CD-RISC; OR = 0.36), and reduced use of positive cognitive emotion regulation strategies, including positive refocusing (CERQ; OR = 0.64) and lower overall positive CERQ (OR = 0.56), were associated with increased risk. In terms of health-related QoL, worse global health status/QoL (EORTC QLQ-C30; OR = 0.97), poorer physical and role functioning (ORs = 0.96–0.97), and greater symptom burden, namely fatigue (OR = 1.03), pain (OR = 1.05), insomnia (OR = 1.02), appetite loss (OR = 1.03), diarrhea (OR = 1.04), and financial impact (OR = 1.03), were also significantly associated with delayed depression, along with greater arm symptoms (BR23; OR = 1.04).

At baseline, core affective symptoms were not significantly associated with delayed depression, including depressive symptoms, anxiety symptoms, and overall mental health distress (HADS). Several coping styles and emotion regulation strategies also showed no significant differences, including forward-, trauma-, total, polarity, and flexibility coping (PACT), self-blame, other-blame, rumination, catastrophizing, perspective-taking, acceptance, planning, and overall negative CERQ, as well as mindfulness (MAAS), coping with cancer (CBI), general self-efficacy, and perceived social support. In addition, fear of cancer recurrence (FCRI), distress thermometer scores (NCCN), negative affect (PANAS), and most breast cancer-specific QoL domains, including body image, treatment side effects, breast symptoms, sexual function, sexual enjoyment, and upset by hair loss (EORTC QLQ-BR23), were not significantly associated. Among EORTC QLQ-C30 domains, cognitive functioning, dyspnea, nausea, and constipation did not differ significantly between groups.

At month 3, psychological distress and affective symptoms were strongly associated with higher odds of belonging to the *Delayed Occurrence of Depression* class, including depressive symptoms (HADS; OR = 9.50), anxiety symptoms (HADS; OR = 5.40), overall mental health distress (HADS total; OR = 17.51), and negative affect (PANAS; OR = 2.13). In contrast, lower positive affect (PANAS; OR = 0.34) and lower emotional and total social support (mMOS; ORs = 0.56–0.56) were associated with reduced odds of delayed depression. Maladaptive coping and behavioral responses were also relevant, with coping by bursting into tears (OR = 1.57) and talking to the physician (OR = 1.69) associated with higher odds.

In terms of health-related QoL, poorer global health status/QoL (EORTC QLQ-C30; OR = 0.97), lower physical, role, emotional, and cognitive functioning (ORs = 0.96–0.98), and greater symptom burden, including nausea (OR = 1.03), pain (OR = 1.02), appetite loss (OR = 1.02), diarrhea (OR = 1.03), and financial impact (OR = 1.02), were significantly associated with delayed depression. Breast cancer-specific domains further characterized this group, including greater arm symptoms (BR23;

OR = 1.03) and poorer future perspective, sexual functioning, and sexual enjoyment (BR23; ORs = 0.97–0.98).

At month 3, several domains did not significantly differentiate the delayed depression and resilient groups, including post-traumatic growth (PTGI), most mental adjustment styles (MAC), family functioning (FARE; although it tends to significance), and general coping resources and behaviors (adherence to medical advice, general self-efficacy, perceived support, and most specific coping strategies). In terms of health-related QoL, social functioning, fatigue, dyspnea, insomnia, and constipation (EORTC QLQ-C30), as well as breast cancer-specific domains such as treatment side effects, breast symptoms, and upset by hair loss (BR23), were not significantly associated.

At baseline, a limited set of features emerged from the stability selection pipeline as robust discriminators between the delayed depression occurrence and resilient groups (Table 7). Among these, only diarrhea, pain, and role functioning demonstrated robust selection, each with 100% selection frequency under both penalized and unpenalized clinical site conditions. In contrast, the selection stability of sense of manageability and optimism declined substantially when clinical site was forced into the model.

At month 3, a broader range of factors differentiated the delayed depression trajectory. Variables showing high selection frequency under both penalized and unpenalized site conditions included diarrhea, emotional functioning, anxiety symptoms, pre-existing mental illness, university education, and coping through communication with the physician, followed by sexual functioning and triple-negative disease. Middle income (vs. low income) showed borderline predictive value, with selection frequency decreasing to approximately 40% after forcing clinical site into the model. Similarly, the stability of unemployment/housewife status and heavy exercise declined markedly once clinical site was unpenalized.

At baseline, the model showed good discrimination and calibration, while at month 3, performance remained stable, with similar probabilistic accuracy and a slightly lower discrimination (Table 7; for chance performance log-loss=0.273 and Brier score=0.072).

Table 7. Stability-selected predictors distinguishing the delayed depression occurrence trajectory class (reference) from the resilient group, with descriptive penalized odds ratios.

Variable	Selection Freq (%)	
	Penalized Site	Unpenalized Site
Baseline		
Performance²: log-loss = 0.248, Brier score = 0.067, ROC-AUC = 0.781		
Diarrhea C30	100%	100%
Manageability SOC	100%	3%
Optimism LOT	100%	10%
Pain C30	100%	100%
Role functioning	100%	97%
Finland (ref. Portugal)	100%	-
Month 3³		
Performance²: log-loss = 0.244, Brier score = 0.066, ROC-AUC = 0.754		
Diarrhea C30	100%	97%
Emotional functioning C30	100%	87%
Mental illness (ref. No)	100%	100%
Triple-negative	100%	60%
Finland (ref. Portugal)	100%	-
University education	100%	93%
Unemployed/Housewife (ref. Full/part-time/Self-employed)	100%	10%
What done to cope: Talked to the physician	100%	87%

Income Middle (ref. Low)	97%	0.8602	40%
Anxiety HADS	93%	1.3522	90%
Sexual functioning BR23	87%	0.9958	73%
Exercise level: Heavy (ref. No)	83%	0.8848	0%
Pain C30	67%	1.0017	13%

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ Depression HADS was not included in the variables at month 3.

3.4.3. Recovery vs Stable Moderate/High

Compared with the Stable Moderate/High Depression class, predictors of belonging to the Recovery Depression class included high income (vs low income; OR = 3.18), HER2-positive disease (OR = 2.56), and luminal B-like (HER2-positive) tumor subtype (OR = 3.94) (Supplementary Figure S16).

At baseline (M0), predictors of belonging to the Recovery Depression class included higher optimism (OR = 2.44), greater sense of coherence–manageability (OR = 1.15), greater sense of coherence–meaningfulness (OR = 1.13), higher mindfulness (OR = 1.87), higher positive affect (OR = 1.90), and lower pain (OR = 0.98) (Supplementary Figure S17).

At Month 3 (M3), predictors of belonging to the Recovery Depression class included lower depressive symptoms (OR = 0.24), lower anxiety symptoms (OR = 0.17), better overall mental health (OR = 0.13), lower spiritual change (PTGI; OR = 0.70), lower helplessness (MAC; OR = 0.36), lower anxious preoccupation (MAC; OR = 0.47), lower distress (NCCN Distress Thermometer; OR = 0.86), higher perceived social support (OR = 1.31), greater treatment control beliefs (OR = 1.28), higher positive affect (OR = 2.19), lower negative affect (OR = 0.49), greater instrumental support (OR = 1.54), greater emotional support (OR = 2.04), greater total social support (OR = 1.90), better emotional functioning (OR = 1.04), better cognitive functioning (OR = 1.02), lower pain (OR = 0.98), lower insomnia (OR = 0.98), fewer arm symptoms (OR = 0.97), and a more positive future perspective (EORTC QLQ-BR23; OR = 1.01) (Supplementary Figure S18).

Based on variable selection method, retained variables at baseline when clinical site was penalized were: sense of manageability, optimism, clinical site (Italy vs Portugal), treatment type (endocrine therapy only vs chemotherapy \pm anti-HER2), and high income (vs low income), all selected in 100% of the stability iterations, followed by residence in Finland (vs Portugal), selected in 60% of iterations.

At month 3, variables selected in 100% of the stability iterations under penalized site conditions included anxiety symptoms, clinical site (Italy vs Portugal), treatment type (endocrine therapy only vs chemotherapy \pm anti-HER2), and high income (vs low income). Variables with high but slightly lower stability included spiritual change, following a special diet, and coping by talking to someone important (each selected in 90% of iterations), as well as emotional functioning. Additional contributors included upset by hair loss, metabolic diseases, residence in Finland (vs Portugal), negative affect, and emotional support (Table 8).

While optimism, income (baseline), endocrine only treatment (baseline and month 3), coping by talking to someone important (month 3), upset by hair image (month 3 and negative affect (month 3) initially demonstrated high selection stability (in the clinical site-penalized model, their selection frequencies dropped dramatically, when site was unpenalized (i.e. forced into the model), indicating that these predictors were site-dependent. In other words, if the models know which clinical site a patient is at, knowing their income or optimism level adds almost no extra predictive value to the specific model.

The selection frequency for Spiritual change (month 3) decreased from 90% (penalized site) to 40% (unpenalized site) and for high income (month 3) from 100% (penalized site) to 57% (unpenalized site). This indicates that while site variation explains a significant portion of the effect

of these variables, a moderate, site-independent effect remains, suggesting this variable possesses a more robust, universal association with the outcome compared to other site-dependent variables.

Although stability analysis identified a consistent set of predictors, overall model discrimination at baseline and month 3 was modest (Table 8; for chance performance log-loss=0.596 and Brier score=0.204), indicating limited predictive capacity. Accordingly, stability-selected variables should be interpreted as robust correlates of the recovery Depression profile.

Table 8. Stability-selected predictors distinguishing the recovery trajectory group (reference) from the stable moderate/high depression group, with descriptive penalized odds ratios.

Variable	Selection Freq (%)	Mean OR ¹	Selection Freq (%)
	Penalized Site	Penalized Site	Unpenalized Site
Baseline			
Performance²: log-loss = 0.575, Brier score = 0.1944, ROC-AUC = 0.664			
Manageability SOC	100%	1.0202	100%
Optimism LOT	100%	1.1608	10%
Italy (ref. Portugal)	100%	0.8259	-
Endocrine only (ref. Chemo only +/-Anti-HER2)	100%	0.8059	7%
Income High (ref. Low)	100%	1.1661	3%
Finland (ref. Portugal)	60%	1.0232	-
Month 3³			
Performance: log-loss = 0.558, Brier score = 0.1869, ROC-AUC = 0.696			
Anxiety HADS	100%	0.6592	97%
Italy (ref. Portugal)	100%	0.7177	-
Endocrine only (ref. Chemo only +/-Anti-HER2)	100%	0.7821	23%
Income High (ref. Low)	100%	1.3056	57%
Spiritual change PTGI	90%	0.9701	40%
Special diet (ref. None)	90%	0.8446	77%
What done to cope: Talked to sb important	90%	1.0455	27%
Emotional functioning C30	87%	1.0028	87%
Upset hair image BR23	80%	1.0012	17%
Metabolic diseases	77%	0.9565	73%
Finland (ref. Portugal)	77%	1.0455	-
Negative affect PANAS	73%	0.9551	0%
Emotional support mMOS	70%	1.0249	87%

¹ Penalized odds ratios are descriptive estimates from elastic net models at the selected λ and are not directly comparable due to differences in variable scaling. ² The performance of the model when clinical site is penalized, i.e. not forced into the model. ³ Depression HADS was not included in the variables at month 3.

4. Discussion

Using latent class growth analysis (LCGA) and growth mixture modeling (GMM), we identified distinct trajectories of C30 Global Health Status/Quality of Life and HADS Depression among women with early breast cancer over an 18-month period following baseline, highlighting clinically meaningful heterogeneity in longitudinal patient-reported outcomes.

Five distinct trajectories of C30 Global Health Status/Quality of Life were identified. Two trajectories reflected stable high functioning, comprising the Good (40.7%) and Excellent (13.2%) groups, whereas nearly one-third of participants belonged to a Moderate trajectory (31.4%)

characterized by persistently intermediate QoL. A small Recovering group (7.8%) demonstrated clear and clinically meaningful improvement over time. Finally, a small but clinically vulnerable subgroup (Low deteriorating, 6.9%) experienced sustained poor QoL with early deterioration and limited recovery.

Park et al. (2023) [48] identified three largely stable QoL trajectories over the first year following the end of primary treatment among breast cancer survivors (N = 124). The majority of women maintained relatively good QoL over time, while a smaller subgroup reported persistently low QoL following treatment. Di Meglio et al. (2022) [49] identified distinct long-term QoL trajectories among women with stage I–III breast cancer treated with adjuvant chemotherapy (N = 4,131), including stable excellent and very good patterns, as well as notably smaller persistently poor and deteriorating trajectories extending up to four years after diagnosis. Goyal et al. (2018) [50] examined quality of life over an 18-month period following baseline assessment (conducted within eight months after diagnosis) among women with newly diagnosed stage I–III breast cancer (N = 653) and identified six trajectories. These included persistently low or very low QoL trajectories, trajectories characterized by moderate or high QoL, as well as two improving trajectories leading to moderate or high QoL, similar to our study.

In the case of depressive symptoms, we identified four distinct trajectories, underscoring clinically meaningful heterogeneity in the longitudinal course of depression. The majority of participants followed a Resilient trajectory (59.7%), characterized by persistently low depressive symptom levels. A substantial proportion belonged to a Stable moderate/high trajectory (25.3%), marked by consistently elevated symptoms indicative of a chronic depressive burden. A smaller Recovering group (10.0%) demonstrated clear and clinically meaningful improvement over time, with symptoms declining to low levels. Finally, a small but clinically vulnerable Delayed occurrence subgroup (5.0%) experienced a gradual and clinically meaningful increase in depressive symptoms during follow-up, reflecting delayed onset of depression.

In a cohort of 4,803 women with stage I–III breast cancer, Charles et al. (2022) [51] examined trajectories of depressive symptoms measured using the Hospital Anxiety and Depression Scale (HADS) over the three years following diagnosis. Six distinct trajectory groups were identified, ranging from persistent non-cases to stable depression. Remission and delayed-onset patterns were identified that comprised only a small proportion of patients, consistent with the findings of the present study. Kant et al. (2018) [52] identified four distress trajectories among 181 newly diagnosed breast cancer patients over the first six months following surgery. A resilient trajectory comprised the majority of patients, whereas high-remitting, delayed, and chronic distress trajectories accounted for smaller proportions, similar to the pattern observed in our study. In 300 Chinese women with breast cancer, Li et al. (2022) [53] reported stable none/mild, stable low and high-decreasing depressive symptom trajectories over 18 months after discharge.

Across these studies, similar to our findings, stable good-QoL or depression trajectories typically comprised the largest proportion of patients, whereas deteriorating or persistently poor QoL trajectories consistently represented smaller but clinically vulnerable subgroups. Differences across studies in the cohort size, baseline timing (before or after the end of primary treatment), study duration, assessment intervals and modelling approach and model selection criteria likely explain the observed variation in the number and type of trajectories reported in the literature, as well as compared to our findings.

To identify parsimonious sets of predictors that jointly differentiate longitudinal quality-of-life and depression trajectory groups, we combined clinically interpretable logistic regression models with multivariable feature selection using elastic net regularization. Following trajectory clustering, individual trajectory classes were retained either to capture nuanced patterns of change in quality of life and depressive symptoms over time or to conduct clinically motivated binary contrasts that support risk stratification and interpretability. For quality of life, comparisons included low-deteriorating versus remaining trajectories, excellent versus remaining trajectories, and recovering versus moderate trajectories, the latter with comparable baseline GHS/QoL levels. For depression,

analyses contrasted the resilient class with the stable moderate/high depression class, the delayed depression occurrence class with the resilient class, and the recovery class with the stable moderate/high depression class. Importantly, all analyses were conducted under two conditions, with the clinical site variable alternatively penalized and left unpenalized, to assess the robustness of predictor selection to potential site effects. Elastic net-penalized logistic regression enabled simultaneous variable selection and coefficient shrinkage, allowing identification of robust predictors while accounting for multicollinearity among candidate psychosocial, clinical, and sociodemographic factors.

Based on clinical-site adjusted univariate logistic regression, Low deteriorating QoL and excellent QoL are largely, but not perfectly mirror images.

Regarding low deteriorating QoL trajectory class, both at baseline and month 3 elastic net feature selection consistently prioritized a short list of variables. At baseline these reflect psychological distress (depressive symptoms, emotional functioning), specific physical symptoms (fatigue, pain, diarrhea), and psychosocial resources (other blame, perceived support, manageability and coping with cancer, exposure to negative life events) irrespective of clinical site penalization, highlighting their robust and site-independent contribution. Clinical factors namely neoadjuvant chemotherapy and triple-negative molecular profile showed an importance however more moderate prediction power. At month 3, the selected predictors were related to functional status (cognitive and physical functioning), psychological symptoms (depressive and anxiety symptoms), beliefs about the control of treatment over the disease and family interpersonal relationships.

Regarding the excellent QoL trajectory, the analysis identified a broad set of robust predictors, strongly suggesting that stronger internal and interpersonal resources, proactive coping strategies, and lower mental distress are closely associated with achieving an excellent quality of life. Moreover, membership in the excellent QoL class reflected a global pattern of sustained superior functioning and lower symptom burden across all QoL domains, evident at both baseline and month 3. In addition, treatment-related factors—including receipt of endocrine therapy and absence of neoadjuvant chemotherapy—together with favorable molecular phenotypes (e.g. Luminal A-like) and selected sociodemographic characteristics (not being unemployed/housewife and not following a vegetarian diet) further contributed to differentiation of the excellent QoL class.

Together, these findings suggest that preventing deterioration is not simply the inverse of promoting excellence. Accordingly, interventions may require distinct emphases and targets, depending on whether the clinical goal is risk mitigation or the promotion of flourishing and optimal quality of life.

Recovery from a moderate QoL trajectory was characterized by a focused profile of adaptive psychological resources, positive affect, and preserved social and sexual functioning, rather than by low psychological distress. At both baseline and month 3, recovery was consistently associated with active and positive coping styles, optimism, mindfulness, personal control beliefs, and self-efficacy, alongside lower pain and better functioning. Socioeconomic factors (namely income) also played a role. Together, these findings suggest that QoL recovery reflects the mobilization of adaptive psychological and functional resources, highlighting targets that may be particularly relevant for interventions aimed at restoring well-being rather than merely preventing decline.

The contrast between the resilient and stable moderate/high depression trajectories was primarily defined by a consistent pattern of psychological vulnerability, functional impairment, and symptom burden. Across baseline and month 3, persistent depression was associated with higher anxiety, distress, negative affect, helplessness, and catastrophizing, alongside poorer emotional, role, and cognitive functioning and greater physical symptoms. In contrast, resilience appeared to be characterized by preserved meaning, optimism, manageability, and emotional functioning, rather than the absence of clinical or treatment-related exposures.

The comparison between the resilient and delayed depression occurrence trajectories suggests that delayed onset of depressive symptoms is less strongly rooted in baseline psychological vulnerability. At baseline, differences were minimal and primarily reflected physical symptoms and

role functioning, whereas by month 3, delayed depression was characterized by worsening emotional functioning, increased anxiety, and greater engagement with illness-related concerns. Delayed depression may reflect a dynamic response to accumulating treatment- and disease-related stressors, rather than pre-existing psychological risk alone.

The contrast between the recovery and stable moderate/high depression trajectories revealed only a limited set of robust predictors once clinical site effects were taken into account. At baseline, sense of manageability emerged as the sole stable psychological factor associated with recovery. By month 3, recovery was primarily differentiated by lower anxiety, better emotional functioning, spiritual change, emotional support, income, and metabolic disease. The dominance of clinical site in these models suggests that country-level contextual factors, such as differences in healthcare systems, cultural norms, social support structures, and treatment pathways, account for a large proportion of the variance between recovery and persistent depression.

The current study extends the findings of a previous analysis by Karademas et.al. (2023) [54] stemming from BOUNCE dataset, which employed a shape-based clustering approach (advanced k-means using *kmlShape* in R [55]) combined with a random forest classifier to identify predictors of dichotomized outcomes. By adopting a more statistically rigorous probabilistic framework, namely Latent Class Growth Analysis (LCGA) and Growth Mixture Modeling (GMM), we moved from distance-based partitioning to model-based clustering, which explicitly accounts for the underlying data distribution and provides a formal basis for class selection through established fit indices. Furthermore, rather than collapsing trajectories into binary endpoints, a practice that can obscure clinically relevant temporal heterogeneity, we retained individual trajectory classes to capture nuanced patterns of change in quality of life and depressive symptoms over time, while conducting clinically motivated binary contrasts (e.g., excellent vs. non-excellent or low-deteriorating vs. remaining trajectories) to support risk stratification analyses. This strategy, combined with Elastic Net regularization, enabled a more stable and interpretable selection of predictors by effectively addressing multicollinearity and mitigating the risk of overfitting and unstable variable selection that can arise in non-parametric tree-based methods, particularly in settings with highly correlated predictors [45,56]. Finally, clinical site heterogeneity was explicitly addressed through secondary stability analyses in which site variables were forced into the model, allowing for the identification of robust, site-independent predictors.

The latent class trajectories identified in this study show strong conceptual alignment with the patterns reported in [54]. Both analyses consistently identified stable high-QoL/low-distress and chronic low-QoL/high-distress groups, as well as trajectories reflecting recovery or delayed response. Differences primarily relate to class composition and size. Recovery and delayed-response classes in the present study were substantially smaller (approximately one-half to one-third) than those reported by Vangelis et al. In addition, we did not identify a delayed-deterioration QoL trajectory (characterized by initially moderate-to-high levels followed by decline) or an “unstable good” V-shaped trajectory attributed to transient treatment effects, although V-shaped patterns were also evident within other trajectories. In the present analysis, mean trajectory shapes cannot exhibit sharp V-shaped patterns, as they are approximated by smooth (linear or quadratic) functions.

Differences primarily reflect the tendency of shape-based clustering to distinguish and group in one class timing-related subpatterns, while the model-based approach assumes groups are defined by shared growth parameters (like specific intercepts and slopes) and accounts for within-class variability.

The *kmlShape* algorithm is designed to identify complex trajectory shapes [55] and preserve it in the mean trajectory. Such an example is a sharp “V-shaped” (drop-then-recovery) patterns that may better reflect short-term treatment effects. However, this approach clusters individuals based on shape similarity alone, regardless of the timing of changes (e.g., whether a decline occurs at month 3 or month 9), and is insensitive to baseline (intercept) differences, as it focuses on relative movements along the path. (e.g. it can recognize that a patient dropping from 80 to 50 and back to 80 has the same V-shape as one dropping from 60 to 30 and back to 60).

In contrast, LCGA/GMM approach is a statistical tool that accounts for uncertainty and individual-level differences within the groups. They are better suited when the timing of changes is clinically meaningful (e.g. does dropping early predict worse outcomes than dropping late?) and due to their parametric formulation, are sensitive to intercept differences (e.g. a “High Baseline” group and a “Low Baseline” group are statistically different populations, even if they share the same slope or recovery shape). Moreover, because GMM typically fits smooth (e.g., quadratic) trajectories, very sharp V-shaped patterns may not be identified as distinct classes and can instead be treated as outliers around a stable underlying trend. Notably, in our results, the excellent QoL trajectory showed no treatment-related decline based on visual inspection of individual-level trajectories (i.e. the methodology distinguished a class that is not affected by treatment), whereas declines at treatment time points were observed across all other classes.

Differences between our findings and those reported by Karademas et al. (2023) likely reflect important methodological distinctions rather than true inconsistencies. In the previous analysis, trajectories were collapsed into dichotomous outcomes, whereas our approach retained multiple, distinct trajectory classes, allowing clinical factors—such as neoadjuvant chemotherapy and triple-negative disease—to emerge as relevant for specific QoL patterns rather than for broad outcome categories. As a result, predictors associated with particular clinical courses may have been obscured in the earlier binary framework. In addition, the use of random forests in the prior study may have influenced variable importance estimates in the presence of highly correlated predictors, where importance can be distributed across correlated features or masked entirely. In contrast, the elastic net framework explicitly addresses multicollinearity, enabling more stable identification of clinical predictors whose effects are conditional on specific trajectory memberships.

There is evidence that suggests that GMM may outperform alternative approaches, including k-means, in certain settings [57–60]. However, further methodological work is needed to clarify the conditions under which different longitudinal clustering methods converge or diverge. Hybrid or comparative frameworks ([57]; *latrend* R package) may offer promising avenues for improving the identification of clinically meaningful longitudinal phenotypes.

Future research must prioritize the early identification of QoL and distress profiles immediately following a breast cancer diagnosis. This period serves as a critical window for proactive risk stratification and the development of personalized supportive care plans. While the majority of patients maintain favorable QoL trajectories, a clinically vulnerable minority experiences persistent or deteriorating functional outcomes that require intensive, targeted intervention.

To improve the precision of these models, larger, well-characterized cohorts are necessary to capture the heterogeneity and temporal dynamics inherent in these high-risk subgroups. Advanced machine learning (ML) approaches, such as XGBoost or Random Survival Forests, offer a unique opportunity to integrate multidimensional factors, including clinical biomarkers, and psychosocial variables. However, researchers must employ robust techniques like Synthetic Minority Over-sampling (SMOTE) [61] or engineered up-sampling (ENUS) [62] to handle significant data imbalance, ensuring that models do not overlook the high-risk minority.

Furthermore, the transition to clinical practice requires interpretable and calibrated prediction frameworks [63]. When paired with interpretable frameworks like SHAP for clinical transparency [64] or Conformal Prediction [65–67] for calibrated risk estimates accompanied by rigorous confidence intervals, ML models can support shared decision-making without the typical opacity of black-box systems, thus, fostering trust in Clinical Decision Support (CDS) tools. By identifying key variables associated with trajectory membership, this analysis lays the foundation for clinically meaningful risk models that support shared decision-making and the efficient allocation of survivorship resources.

4.1. Strengths and Limitations

The methodological approach has several key strengths. Stability analysis across multiple imputations and repeats ensures findings are reliable, not accidental results from a single data version

or data partition. Elastic Net ($\alpha=0.5$) manages correlated clinical variables effectively. This prevents the model from arbitrarily picking one and ignoring the other, unless one is clearly a redundant proxy. Forcing clinical sites into the model is a critical “stress test” that identifies truly universal predictors by removing clinical site/country-specific bias and institutional confounding. The use of the $\lambda=1se$ rule results in a simpler, more interpretable model that is less likely to overfit and more likely to generalize to new patient populations.

Several limitations should be considered when interpreting the findings. Prediagnosis levels of psychological variables were not available, limiting our ability to distinguish cancer-related changes from pre-existing conditions. Not all variables were assessed at baseline and month 3, which may have constrained the temporal resolution of the analyses. Differences across clinical sites, including variations in care pathways and cultural contexts, may have contributed to heterogeneity in patient-reported outcomes despite adjustment for site effects. In addition, the small sample sizes in specific trajectory classes may have constrained the stability of the model, increasing the risk of overfitting and limiting the generalizability of predictors identified within these smaller cohorts. Finally, some analyses were cross-sectional in nature, which precludes causal inference.

5. Conclusions

Findings suggest that heterogeneous subgroups of patients follow distinct adjustment pathways over time, with differences explained by variations in symptom burden, functional scales, coping styles and affect. These results provide insights into the multidimensional determinants of resilience and highlight potential intervention targets to support individualized care and long-term quality of life and mental health in women with breast cancer.

Supplementary Materials: The following supporting information can be downloaded at: <https://zenodo.org/records/18209914>.

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Informed Consent Statement: Informed consent was obtained from all patients involved in the study.

Data Availability Statement: The anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request. Data are not publicly accessible due to ethical and privacy constraints..

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Abbreviations

The following abbreviations are used in this manuscript:

BR23	BReast cancer-specific module of EORTC QLQ
CBI-B	Cancer Behavior Inventory
CD-RISC	Connor-Davidson Resilience Scale
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life
QLQ-C30	Questionnaire - Core 30
FCR-SF	Fear of Cancer Recurrence Scale-Short Form
GHS/QoL	Global Health Status/ QoL scale of EORTC-QLQ-C30
HADS	Hospital Anxiety and Depression Scale
LOT	Life Orientation Test
MAAS	Mindful Attention Awareness Scale
MAC	Mental Adjustment to Cancer Scale
MOS	Medical Outcomes Study
PACT	Perceived Ability to Cope with Trauma Scale
PANAS	Positive and Negative Affect Schedule
PTGI-SF	Post-Traumatic Growth Inventory-Short Form
QoL	Quality of Life
SOC	Sense of Coherence Scale

Appendix A

Selection of Link Function

Non-normality of the longitudinal outcomes (C30 global health/QoL, HADS Depression) is addressed by transforming the data using a non-linear link function (or latent process) from the *lcmm* package in R. The method simultaneously estimates the parameters of the link function and the latent process mixed model using maximum likelihood. To identify the most suitable link function, null models (i.e. with one latent class) are fit to the data, considering various non-linear link functions. Specifically, the beta cumulative distribution and I-splines differing in the number and placement of knots are explored. The I-spline associated with the lowest BIC value is selected for the final analysis. Based on Tables A1-A4, the model with a link function approximated by I-splines with 6 knots placed at the quantiles of the outcome distribution provides the best fit.

Table A1. Comparison of C30 GHS/QoL LCGA Models with One Latent Class and Different Link Functions.

Transformation - link function	AIC	BIC
None	30481.32	30498.47
Beta cumulative distribution	29468.93	29494.65
I-splines with 5 equidistant knots	30001.87	30040.46
I-splines with 5 knots at quantiles	29889.07	29927.66
I-splines with 6 equidistant knots	29997.34	30040.21
I-splines with 6 knots at quantiles	29412.77	29455.64
I-splines with 7 equidistant knots	29955.92	30003.08
I-splines with 7 knots at quantiles	29411	29458.16

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Table A2. Comparison of C30 GHS/QoL GMM Models with One Latent Class and Different Link Functions.

Transformation - link function	AIC	BIC
None	28905.96	28948.84
Beta cumulative distribution	27780.27	27831.73
I-splines with 5 equidistant knots	28306.42	28370.74

I-splines with 5 knots at quantiles	28193.4	28257.72
I-splines with 6 equidistant knots	28300.39	28369
I-splines with 6 knots at quantiles	27722.3	27790.9
I-splines with 7 equidistant knots	28258.61	28331.5
I-splines with 7 knots at quantiles	27719.66	27792.55

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Table A3. Comparison of HADS Depression LCGA Models with One Latent Class and Different Link Functions.

Transformation - link function	AIC	BIC
None	5384.34	5401.491
Beta cumulative distribution	3830.596	3856.323
I-splines with 5 equidistant knots	3459.454	3498.045
I-splines with 5 knots at quantiles	3344.796	3383.387
I-splines with 6 equidistant knots	3423.261	3466.14
I-splines with 6 knots at quantiles	3340.9	3383.778
I-splines with 7 equidistant knots	3398.965	3446.132
I-splines with 7 knots at quantiles	3339.337	3386.504

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Table A4. Comparison of HADS Depression GMM Models with One Latent Class and Different Link Functions.

Transformation - link function	AIC	BIC
None	2688.547	2731.426
Beta cumulative distribution	1272.653	1324.107
I-splines with 5 equidistant knots	976.3214	1040.639
I-splines with 5 knots at quantiles	882.3571	946.675
I-splines with 6 equidistant knots	955.6132	1024.219
I-splines with 6 knots at quantiles	869.0842	940.7354
I-splines with 7 equidistant knots	941.1433	1014.037
I-splines with 7 knots at quantiles	869.0842	941.9778

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Appendix B

Trajectory Clustering of C30 GHS/QoL

As shown in Table B1, fit indices suggest different optimal LCGA solutions: AIC favors the eight-class model, BIC supports the seven-class model and ICL indicates the six-class solution. Estimated trajectories for the two- to eight-class models are shown in Figure B1. All models meet the minimum class-size criterion (>5%). However, posterior probabilities in the seven- and eight-class solutions are near or below the 0.7 threshold for some classes, indicating poor class separation and reduced assignment certainty; these solutions are therefore not retained for further interpretation.

Visual inspection of the two- to six-class solutions reveals consistent and clinically meaningful trajectory patterns (Figure B1). Across all models, a resilient high GHS/QoL trajectory is observed, while a persistently poor and declining trajectory emerges from the four-class solution onward. An additional recovering trajectory is identified in the five- and six-class models. The remaining classes in the five- and six-class solutions exhibit largely stable trajectories that differed primarily in baseline C30 GHS/QoL levels. The six-class solution adds a class with a trajectory pattern already captured in the five-class model, providing limited additional clinical value.

Using the GMM approach, the best fitting model based on BIC and ICL is the null model, i.e. no latent classes, while the AIC favors the five-class solution (Table B2). However, because two classes in the five-class model comprise fewer than 5% of the sample, the four-class solution is preferred. Classification quality of four-class model is acceptable, with posterior probabilities exceeding the 0.70 threshold for all classes.

Figure B2 presents the estimated trajectories of two- to six- class solutions with the highest loglikelihood. From the three-class solution onward, two characteristic trajectories consistently emerge: a resilient trajectory characterized by persistently high GHS/QoL scores and a persistently poor trajectory with declining scores over time. These trajectories are also identified in the LCGA results. In the four-class solution the remaining patients are split into two groups with slightly improving or steady trajectories that primarily differ in baseline C30 GHS/QoL levels. In the three-class solution, these two groups are combined into a single trajectory. Notably, the recovering trajectory observed in the LCGA analyses does not emerge in the GMM models, although small recovering classes (<5%) appear in the five- and six-class solutions. Patients who comprise the recovering trajectory in the LCGA are primarily classified within the resilient trajectory in the GMM models.

Taking into account statistical fit, class separation, parsimony and clinical interpretability, the LCGA five-class solution was selected as the optimal model. This solution captured all clinically interesting trajectory patterns while maintaining clear class differentiation and interpretability. Classification quality of the model is good, with posterior probabilities exceeding 0.8 for all classes (Table B3).

Table B1. Goodness of fit statistics for C30 GHS/QoL LCGA model solutions and proportion of each class.

No of classes	loglik	AIC	BIC	entropy	ICL	Relative class size (%)							
						class 1	class 2	class 3	class 4	class 5	class 6	class 7	class 8
1	-	2941	2945	1	2945	100	-	-	-	-	-	-	-
	14696	3	6		6								
2	-	2836	2842	0.857	2848	32.16	67.84	-	-	-	-	-	-
	14170	8	8		1								
3	-	2795	2803	0.836	2812	19.89	52.79	27.32	-	-	-	-	-
	13959	5	2		9								
4	-	2786	2795	0.809	2809	16.36	29.55	6.32	47.77	-	-	-	-
	13908	1	5		8								
5	-	2778	2790	0.800	2807	13.20	40.71	7.81	31.41	6.88	-	-	-
	13869	9	1		4								
6	-	2773	2786	0.795	2805	10.22	12.27	7.06	41.64	23.42	5.39	-	-
	13836	2	0		8								
7	-	2770	2785	0.768	2809	10.04	11.52	35.50	6.51	23.05	8.36	5.02	-
	13820	8	4		7								
8	-	2770	2786	0.726	2817	9.85	11.71	35.13	8.55	10.41	6.51	12.45	5.39
	13815	6	8		5								

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ICL: Integrated Complete Likelihood.

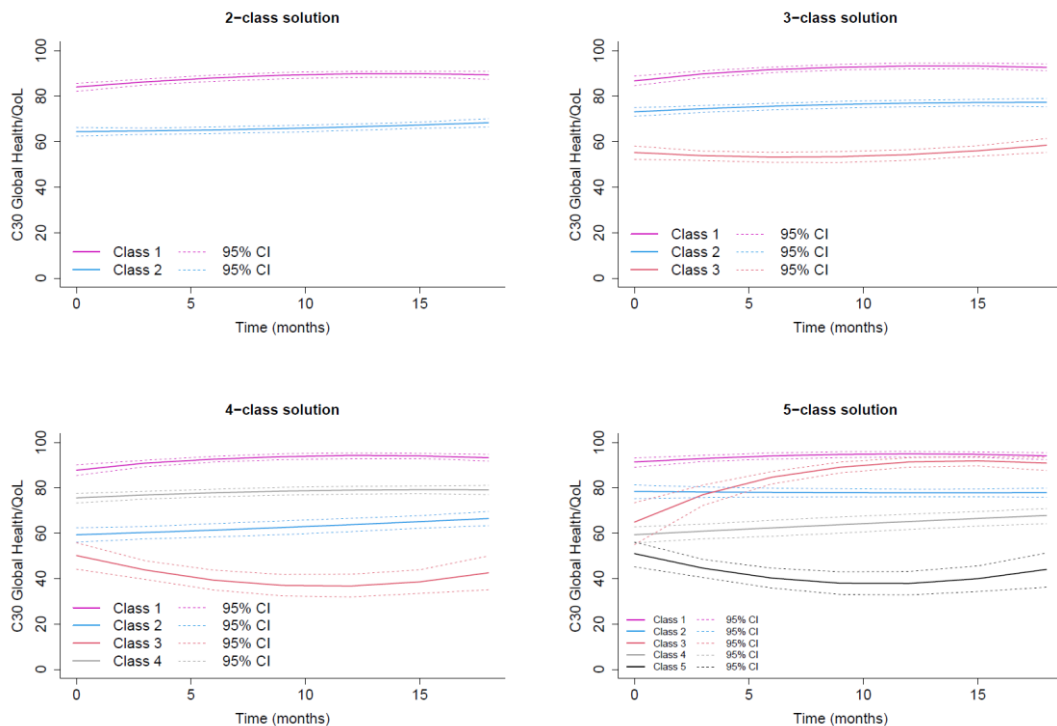
Table B2. Goodness of fit statistics for C30 GHS/QoL GMM model solutions and proportion of each class.

No of classes	loglik	AIC	BIC	entropy	ICL	Relative class size (%)					
						class1	class2	class3	class4	class5	class6
1	-13845	27722	27791	1	27791	100	NA	NA	NA	NA	
2	-13841	27722	27808	0.504	27993	22.68	77.32	NA	NA	NA	NA
3	-13831	27710	27813	0.766	27951	7.99	19.14	72.86	NA	NA	NA
4	-13825	27706	27826	0.713	28040	46.28	5.58	17.47	30.67	NA	NA
5	-13819	27702	27839	0.759	28048	3.35	15.61	69.70	8.18	3.16	NA
6	-13816	27704	27858	0.731	28118	17.47	44.61	1.12	28.81	5.95	2.04

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ICL: Integrated Complete Likelihood.

Table B2. Average of posterior probabilities in each class for C30 GHS/QoL LCGA five-class solution.

Assigned class	Class 1 Excellent GHS/QoL	Class 2 Good GHS/QoL	Class 3 Recovering GHS/QoL	Class 4 Moderate GHS/QoL	Class 5 Low deteriorating GHS/QoL
1	0.9222	0.0378	0.0400	0.0000	0.0000
2	0.0093	0.8547	0.0338	0.1022	0.0000
3	0.0657	0.1222	0.8002	0.0118	0.0000
4	0.0000	0.0944	0.0047	0.8636	0.0373
5	0.0000	0.0000	0.0000	0.0808	0.9192



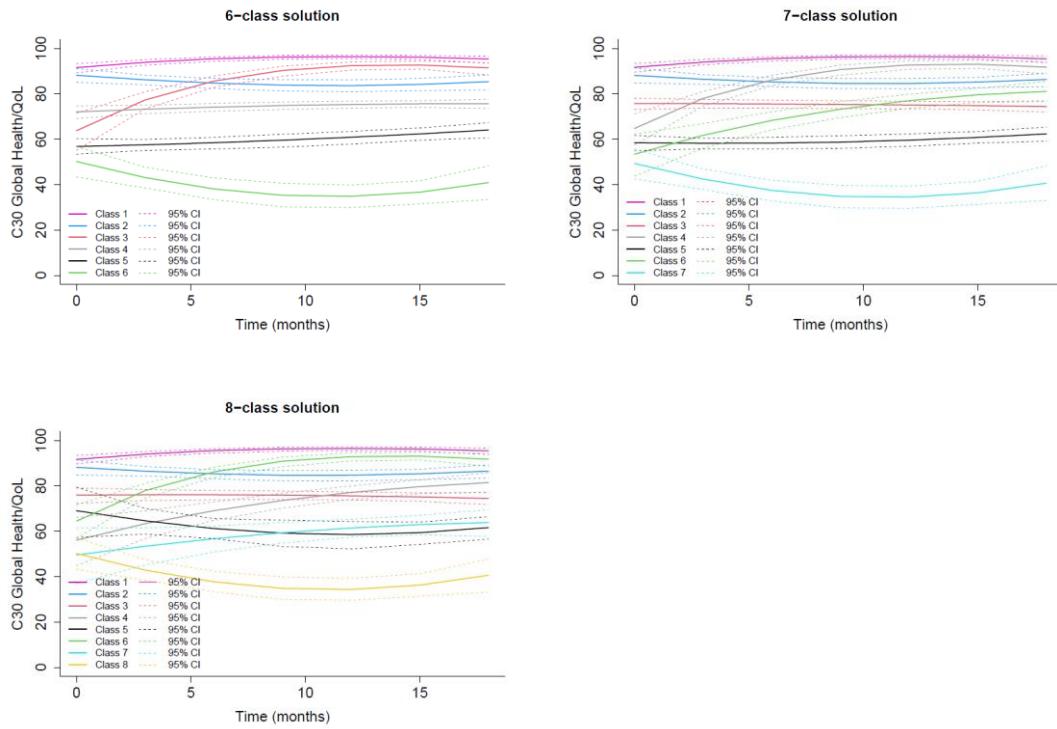
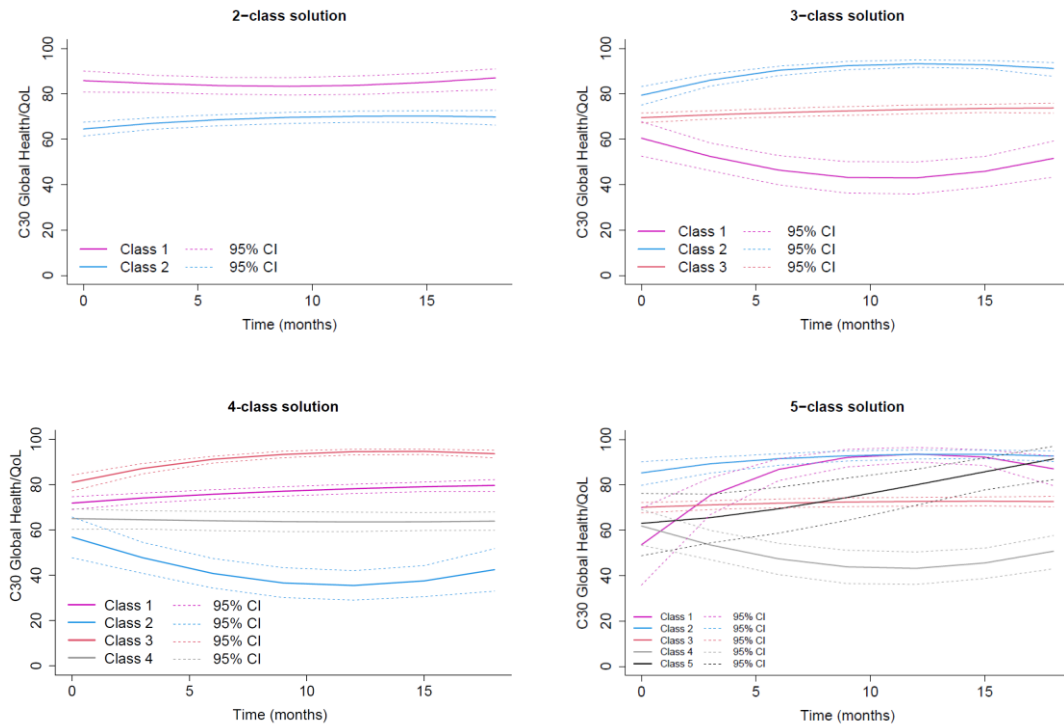


Figure B1. Estimated average C30 GHS/QoL trajectories for two- to eight-class solutions, shown for the LCGA approach.



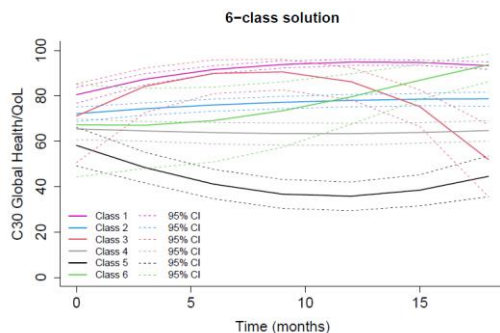


Figure B2. Estimated average C30 GHS/QoL trajectories for two- to eight-class solutions, shown for the GMM approach.

Appendix C

Trajectory Clustering of HADS Depression

The best-fitting LCGA model according to AIC and BIC is the eight-class solution, whereas ICL favors the six-class model (Table C1). However, in the five- to eight-class solutions, the smallest class comprises less than 5% of the sample, making these models unsuitable for further analysis.

In the two-, three- and four-class solutions, the classes exhibit very similar trajectory shapes (Figure C1). Their average trajectories remain largely steady over the 18-month period, with the exception of the class with the highest baseline depression scores, which shows a modest increase. Consequently, most trajectories are nearly parallel, differing primarily in baseline depression levels, all of which are below the clinically meaningful threshold of 1. From a clinical perspective, reassigning patients with depression scores below this threshold provides little added value.

Using the GMM approach, the best fitting model according to BIC and ICL is the null model, i.e. no latent classes, while the AIC indicates the six-class solution (Table C2). However, in the six- and five-class solutions, the size of the smallest class falls below 5% of the sample, making the four-class solution preferred choice. Classification quality of four-class model is acceptable, with posterior probabilities exceeding the 0.70 threshold for all classes.

Visual inspection of the four-class solution (Figure C2) reveals clinically meaningful trajectory patterns that were also present in solutions with a higher number of classes: two stable trajectories, one at low depression scores and one around a score of 1, as well as a low-worsening trajectory and an high-improving trajectory. Remarkably, the improving trajectory is also identified in the LCGA solutions with six or more classes.

Considering both statistical fit and clinical relevance, the four-class GMM solution was selected as optimal. This model encompassed all clinically important trajectory patterns while keeping class membership easily interpretable. Classification quality of the model is acceptable, with posterior probabilities exceeding 0.75 for all classes (Table C3).

Table C1. Goodness of fit statistics for HADS Depression LCGA model solutions and proportion of each class.

No of classes	loglik	AI C	BI C	entropy	IC L	%class s1	%class s2	%class s3	%class s4	%class s5	%class s6	%class s7	%class s8
1	-	33	33	1	33	100	NA	NA	NA	NA	NA	NA	NA
	1660	41	84		84								
2	-861	17	18	0.899	18	47.21	52.79	NA	NA	NA	NA	NA	NA
		50	10		48								

3	-631	12	13	0.873	14	19.70	38.48	41.82	NA	NA	NA	NA	NA
		98	75		50								
4	-553	11	12	0.845	13	16.54	33.64	37.92	11.90	NA	NA	NA	NA
		49	43		59								
5	-497	10	11	0.851	12	3.53	37.17	17.47	30.67	11.15	NA	NA	NA
		47	58		87								
6	-455	97	10	0.843	12	3.53	17.47	6.88	28.81	30.67	12.64	NA	NA
		1	99		51								
7	-434	93	10	0.798	12	3.53	22.12	7.62	15.99	16.36	10.78	23.61	NA
		6	82		93								
8	-412	90	10	0.809	12	2.60	7.62	23.05	1.12	23.79	10.59	15.61	15.61
		0	63		77								

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ICL: Integrated Complete Likelihood.

Table C2. Goodness of fit statistics for HADS Depression GMM model solutions and proportion of each class.

No of class	Relative class size (%)										
	loglik	AI	BIC	entropy	ICL	%class1	%class2	%class3	%class4	%class5	%class6
1	-420	872	941	1	941	100	NA	NA	NA	NA	NA
2	-410	860	946	0.586	1101	21.93	78.07	NA	NA	NA	NA
3	-403	854	957	0.657	1159	2.60	23.79	73.61	NA	NA	NA
4	-391	838	958	0.681	1196	10.04	5.02	59.67	25.28	NA	NA
5	-383	829	966	0.732	1199	4.28	25.09	60.04	9.85	0.74	NA
6	-373	819	973	0.772	1193	3.72	51.67	33.83	1.67	8.36	0.74

Note: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ICL: Integrated Complete Likelihood.

Table C3. Average of posterior probabilities in each class for HADS Depression GMM four-class solution.

Assigned class	Class 1 Recovery	Class 2 Delayed occurrence	Class 3 Resilient	Class 4 Stable Moderate/High
1	0.7735	0.0000	0.1608	0.0657
2	0.0000	0.7899	0.1206	0.0895
3	0.0375	0.0090	0.8620	0.0914
4	0.0353	0.0348	0.1760	0.7540

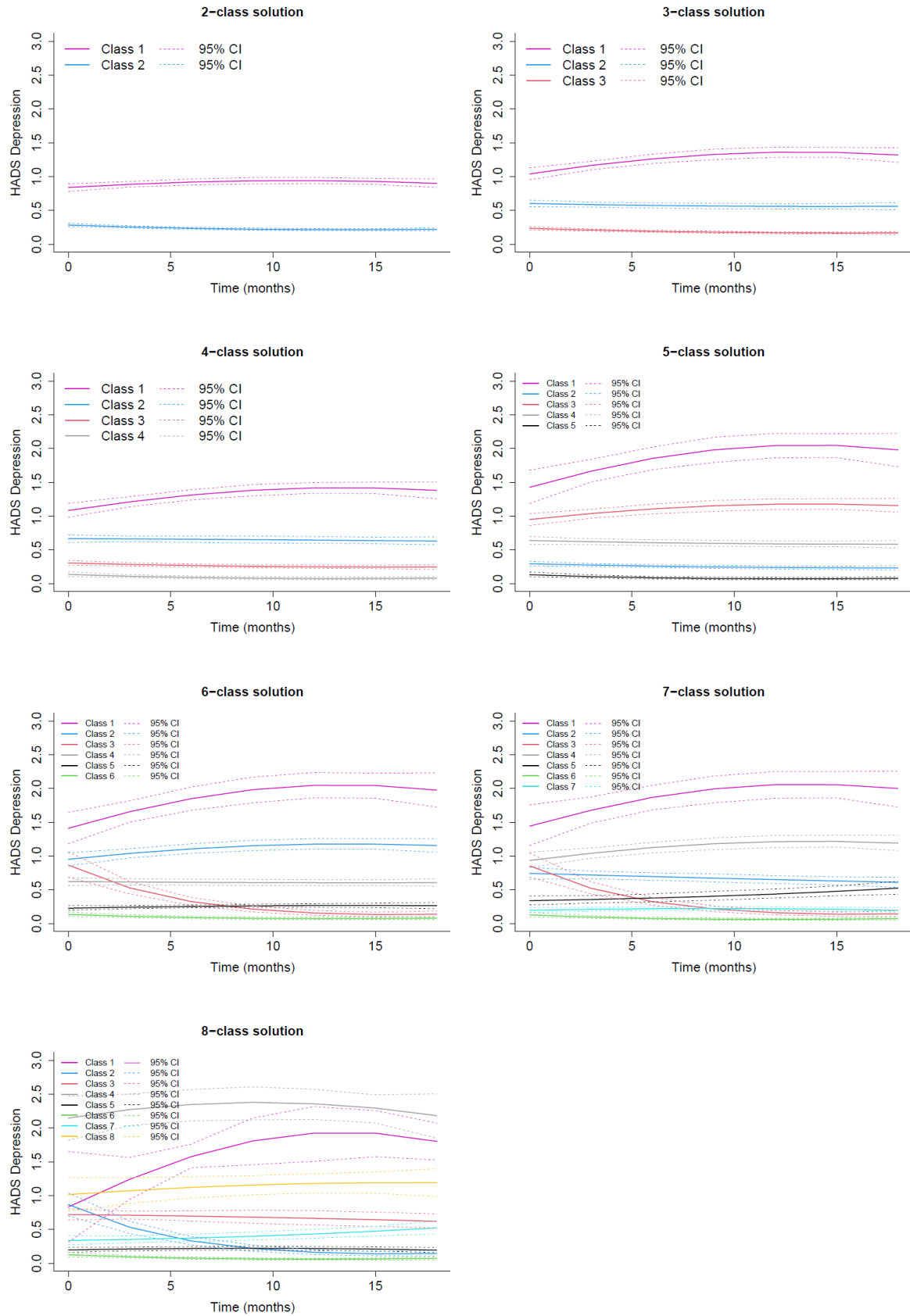


Figure C1. Estimated average HADS Depression trajectories for two- to eight-class solutions, shown for the LCGA approach.

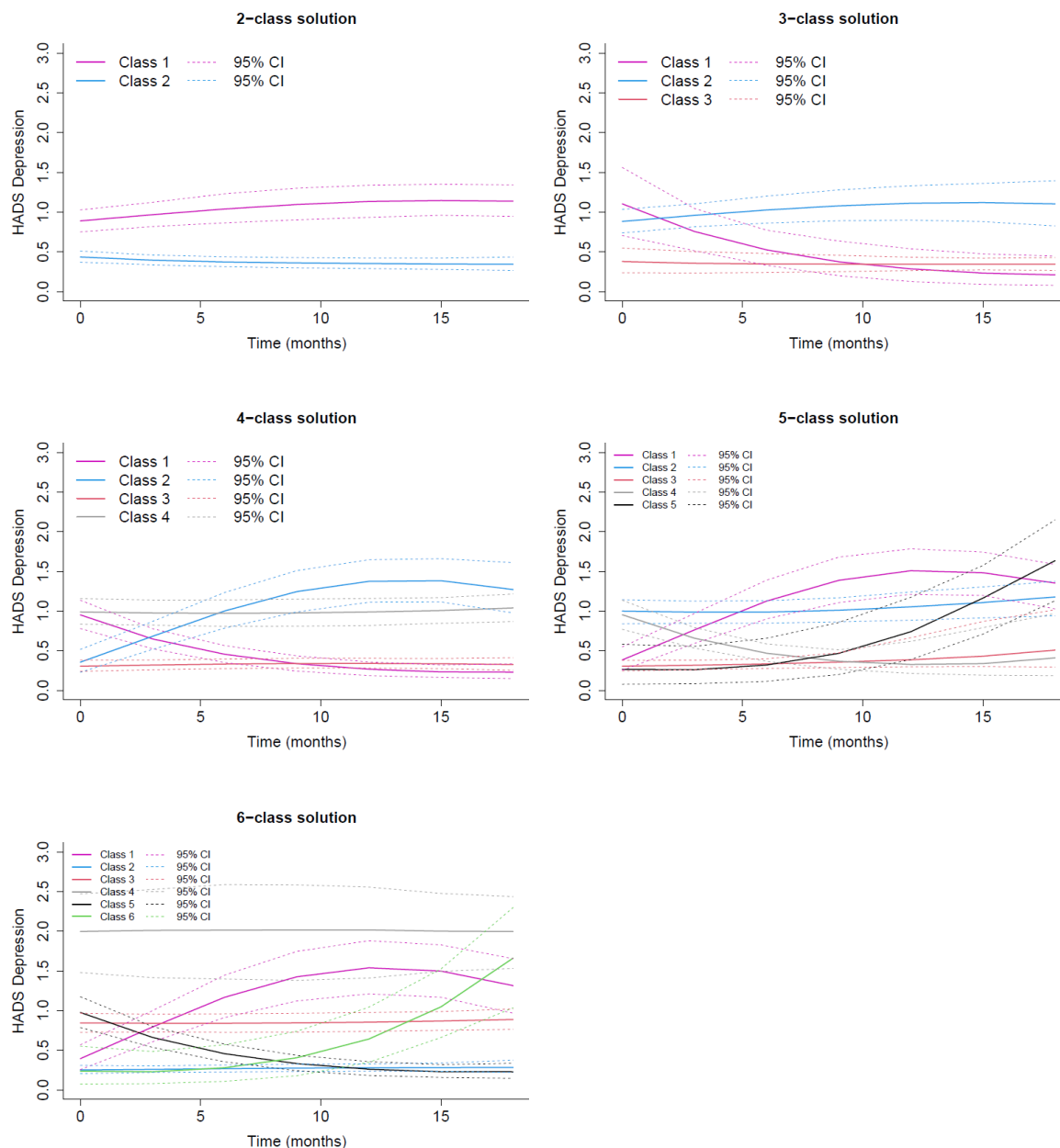


Figure C2. Estimated average HADS Depression trajectories for two- to six-class solutions, shown for the GMM approach.

Appendix D

Table D1. Maximum Likelihood Estimates for the selected C30 GHS/QoL five-class model. The Table presents estimated parameters, standard errors (SE), the Wald test statistics and corresponding p value. The Wald test assesses whether each parameter differs significantly from zero. Classes 1, 2, 3, 4 and 5 correspond to the Excellent, Good, Recovering, Moderate and Low deteriorating C30 GHS/QoL trajectory latent classes, respectively.

Fixed effects in the class-membership model:

(the class of reference is the last class)

	coefficient	SE	Wald	p-value
intercept class 1	0.55548	0.28801	1.929	0.05378
intercept class 2	1.65476	0.30204	5.479	0.00000

intercept class 3	0.10195	0.35111	0.290	0.77153
intercept class 4	1.44951	0.23372	6.202	0.00000
Fixed effects in the longitudinal model:				
	coefficient	SE	Wald	p-value
intercept class1 (not estimated)	0			
intercept class 2	-1.34743	0.18936	-7.116	0.00000
intercept class 3	-2.39865	0.28857	-8.312	0.00000
intercept class 4	-2.74885	0.18200	-15.103	0.00000
intercept class 5	-3.26800	0.21464	-15.226	0.00000
linear slope class 1	0.09053	0.03134	2.889	0.00386
linear slope class 2	-0.00849	0.02040	-0.416	0.67729
linear slope class 3	0.34277	0.06492	5.280	0.00000
linear slope class 4	0.03283	0.02206	1.488	0.13668
linear slope class 5	-0.13893	0.04217	-3.295	0.00099
quadratic slope class 1	-0.00378	0.00164	-2.305	0.02117
quadratic slope class 2	0.00033	0.00101	0.329	0.74253
quadratic slope class 3	-0.01185	0.00300	-3.945	0.00008
quadratic slope class 4	-0.00008	0.00116	-0.070	0.94426
quadratic slope class 5	0.00651	0.00222	2.934	0.00335
Parameters of the link function:				
	coefficient	SE	Wald	p-value
I-splines 1	-5.95455	0.21304	-27.950	0.00000
I-splines 2	1.06674	0.09931	10.742	0.00000
I-splines 3	0.91341	0.09308	9.813	0.00000
I-splines 4	1.42070	0.03349	42.424	0.00000
I-splines 5	0.86157	0.02925	29.451	0.00000
I-splines 6	-1.17587	0.02114	-55.617	0.00000
I-splines 7	0.00011	0.03728	0.003	0.99767
I-splines 8	-0.95530	0.02128	-44.889	0.00000

Table D2. Maximum Likelihood Estimates for the selected HADS Depression four-class model. The Table presents estimated parameters, standard errors (SE), the Wald test statistics and corresponding *p* value. The Wald test assesses whether each parameter differs significantly from zero. Classes 1, 2, 3 and 4 correspond to the Recovery, Delayed Occurrence, Resilient and Stable/High Depression trajectory latent classes, respectively.

Fixed effects in the class-membership model:				
(the class of reference is the last class)				
	coefficient	SE	Wald	p-value
intercept class 1	-0.85515	0.34940	-2.448	0.01438
intercept class 2	-1.56106	0.40570	-3.848	0.00012
intercept class 3	0.81867	0.29328	2.791	0.00525
Fixed effects in the longitudinal model:				
	coefficient	SE	Wald	p-value
intercept class1 (not estimated)	0			

intercept class 2	-2.12840	0.43187	-4.928	0.00000
intercept class 3	-2.40407	0.29120	-8.256	0.00000
intercept class 4	0.11938	0.33984	0.351	0.72537
linear slope class 1	-0.35787	0.05419	-6.605	0.00000
linear slope class 2	0.47814	0.07396	6.465	0.00000
linear slope class 3	0.01588	0.02306	0.689	0.49109
linear slope class 4	-0.02495	0.03805	-0.656	0.51200
quadratic slope class 1	0.01082	0.00267	4.052	0.00005
quadratic slope class 2	-0.01737	0.00388	-4.478	0.00001
quadratic slope class 3	-0.00075	0.00125	-0.604	0.54560
quadratic slope class 4	0.00171	0.00216	0.792	0.42858

Variance-covariance matrix of the random-effects:

	intercept	linear slope	quadratic slope
intercept	0.89100		
linear slope	0.03042	0.00566	
quadratic slope	-0.00159	-0.00025	1e-05

Parameters of the link function:

	coefficient	SE	Wald	p-value
I-splines 1	-4.61362	0.28054	-16.446	0.00000
I-splines 2	0.95180	0.02099	45.347	0.00000
I-splines 3	0.79402	0.03608	22.006	0.00000
I-splines 4	1.17562	0.02950	39.851	0.00000
I-splines 5	0.93434	0.03303	28.292	0.00000
I-splines 6	1.61728	0.04373	36.986	0.00000
I-splines 7	1.24502	0.11248	11.069	0.00000
I-splines 8	1.15337	0.13638	8.457	0.00000

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