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Anxiety trajectories and early high anxiety risk identification in ≤ 1cm highly suspicious thyroid nodules under active surveillance

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Abstract

Background

Anxiety is common during active surveillance (AS), but its dynamic changes and impacts on quality of life (QOL) and treatment decisions remain poorly characterized, limiting the development of evidence-based psychological intervention strategies.

Methods

This prospective cohort study enrolled 753 patients with highly suspicious thyroid nodules (≤ 1cm) undergoing AS at Peking Union Medical College Hospital (Nov 2018 - Aug 2025), with 663 were finally analyzed. Anxiety and QOL were assessed using HADS-A and EORTC QLQ-C30. Anxiety trajectories were identified by latent class growth modeling. QOL and conversion surgery rates were analyzed using mixed linear and Fine-Gray models. A logistic regression model base on baseline and 3–6 month HADS-A change (Δscores) was developed to identify high anxiety risk patients, with performance and clinical value evaluated by statistical comparisons and decision curve analysis.

Results

Among 663 patients (median follow-up: 32.6 months), four trajectories were identified: persistently high, worsening, improving, and persistently low, with 22.3% further classified as high anxiety risk (persistently high + worsening). Comparing to low anxiety risk group (persistently low + improving), high anxiety risk group had higher baseline HADS-A scores (6.9 ± 3.0 vs 3.0 ± 2.5) and greater proportion scoring ≥ 8 (39.2% vs 5%, both $p < 0.001$), with similar differences at 36 months. High anxiety risk patients consistently reported worse QOL, especially in emotional function, insomnia, cognitive function, fatigue, and global health status (all $p < 0.001$). Overall conversion surgery rates were similar, but non-disease-related conversion surgery rates were higher in high anxiety risk group ($p = 0.068$). Both baseline HADS-A (OR = 2.366) andΔscore (OR = 2.123) were independent associated with high anxiety risk. The model showed excellent discrimination (AUC = 0.924), superior to the baseline-only model ($p < 0.001$), with greater net clinical benefit than "treat all" or "treat none" strategies.

Conclusion

Anxiety during AS is heterogenous, with nearly one-quarter of patients experiencing persistently or elevated anxiety and poorer QOL. Combining baseline and early HADS-A changes enables effective early identification of these patients, providing a theoretical basis for targeted psychological interventions during AS.

1. Background

The global incidence of thyroid cancer has been sharply risen in recent years. According to the latest epidemiological data, 821,000 new cases of thyroid cancer were diagnosed worldwide in 2022, making it the seventh most prevalent among all malignancies, and one of the fastest-growing cancers globally.[1] Papillary thyroid carcinoma (PTC) is the most common subtype, and accounts for approximately 84% of all cases.[2] Most PTCs are indolent and associated with excellent long-term survival, particularly low-risk PTCs with tumor diameters ≤ 1 cm that account for up to 58.2% of all cases, have a high 20-year survival rate of 99.1%.[3] Therefore, active surveillance (AS) has been widely recommended as a non-surgical management strategy for these patients. By monitoring nodule changes through regular imaging and clinical follow-up, AS allow patients to avoid unnecessary surgery and related complications, reducing overtreatment and unwarranted use of medical resources. With multiple studies supporting its safety and efficacy, AS has been increasingly adopted across many countries and regions worldwide.[4–7]

However, not all eligible patients are willing to accept AS as their management strategy. Studies showed that patients with thyroid nodules frequently experience a spectrum of negative psychological responses, including anxiety, depression, and cancer-related fear when faced with uncertainty or malignant diagnosis, which substantially lowers their acceptance of AS and drives some toward surgical intervention.[8–10] Furthermore, most patients who decline AS attribute their decision primarily to tumor-related psychological distress and negative emotions.[11] In addition, a proportion of patients who initially choose AS may switch to surgery due to persistent fear or chronic anxiety rather than disease progression. These patients often result in worse postoperative quality of life (QOL) and mental health.[12] Therefore, for these patients with malignant tumors but favorable long-term survival, the management process is similar to that of a chronic disease, wherein psychological status plays a pivotal role in both treatment decision-making and long-term QOL outcomes, and fundamental to comprehensive disease management.

Although the psychological well-being of patients during AS has received increasing attention, with anxiety identified as one of the most frequently reported psychological outcome,[13–14] the incidence, dynamic changes, duration, and the impact on quality of life and treatment decision-making remain poorly characterized. This gap precludes evidence-based recommendations regarding the necessity, optimal timing, and target population for psychological interventions in this clinical setting.

The American Thyroid Association (ATA) guidelines have established an ultrasound-based malignancy risk stratification system, in which highly suspicious ultrasound features demonstrate high diagnostic accuracy for thyroid malignancy.[6,15] Given that current guidelines do not recommend routine fine-needle aspiration biopsy (FNAB) for thyroid nodules ≤ 1 cm, and that Chinese patients often express concerns regarding invasive procedures such as biopsy, the diagnosis of benign and malignant nodules in these patients is largely based on ultrasonographic features in clinical practice. Therefore, in this study, we examined patients with sub-centimeter highly suspicious thyroid nodules who met AS criteria based on

ultrasound evaluation. We systematically assessed the incidence and dynamic trajectories of anxiety during AS, identified subgroups with different anxiety patterns, examined the impact of anxiety on QOL and treatment decision-making, and developed an early identification model for patients at high anxiety risk, aiming to provide a scientific basis for individualized management and targeted psychological interventions in clinical practice.

2. Methods

2.1 Study population

This prospective study was conducted at Peking Union Medical College Hospital (PUMCH) from November 2018 to August 2025. A total of 753 patients with highly suspicious malignant thyroid nodules who chose AS were consecutively enrolled. The inclusion criteria were as follows: (1) maximum nodule diameter ≤ 1 cm; (2) nodules classified as highly suspicious for malignancy by ultrasound or cytologically confirmed as PTC by fine-needle aspiration according to ATA guidelines[16]; (3) no evidence of extrathyroidal extension, clinical lymph node metastasis or distant metastasis, with no nodules adjacent to critical structures such as the recurrent laryngeal nerve, trachea, or esophagus; and (4) willingness to provide written informed consent after being fully informed of relevant risks, and completion of baseline psychological and QOL questionnaires. Exclusion criteria were as follows: (1) previous surgery for malignant thyroid tumors; (2) diagnosis of psychiatric or psychological disorders; (3) significant thyroid dysfunction (hyperthyroidism or hypothyroidism) confirmed by serum thyroid function tests; and (4) inability to adhere to long-term AS, lack of at least one post-baseline psychological assessment, or loss to follow-up. Ultimately, 663 patients met all criteria and were included in the analysis. The study flowchart is shown in Fig. 1.

2.2 Clinical disclosure and protocol

At enrollment, all patients were provided with a standardized clinical disclosure by the same team of clinicians. The disclosure included: (1) an explanation that their thyroid nodules were clinically diagnosed as low-risk papillary thyroid microcarcinoma, regardless of whether FNAB had been performed; (2) a detailed discussion of the available treatment options, including AS and immediate surgery, along with the respective benefits, risks, and expected treatment outcomes of each approach; and (3) clarification that both treatment options required regular follow-up, and that during AS, conversion to surgery would be recommended if indications for surgical intervention were identified,[17] with FNAB required prior to surgery to confirm the diagnosis. At each follow-up visit, patients were informed of their ultrasound findings, including changes in nodule size and the appearance of any suspicious lymph nodes, and shared decision-making regarding continuation of AS or conversion to surgery was conducted accordingly.

For patients who consented to participate and signed the informed consent form, the initial psychological and QOL assessments were completed at enrollment, followed by a second assessment

at 3–6 months, and subsequent assessments every 6–12 months thereafter. The number of patients who completed the questionnaires at each time point is provided in Supplementary Table 1.

2.3 Questionnaires

Anxiety status and QOL were assessed using the Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A) and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), respectively. The HADS was specifically designed for use in non-psychiatric medical settings and excludes somatic symptoms that may overlap with physical illness, making it particularly suitable for cancer patients. The HADS-A includes 7 items focusing on anxiety-related symptoms and the scores are interpreted as follows: 0–7 indicates no clinically significant anxiety, 8–10 suggests possible anxiety that requires further psychiatric evaluation, and 11 or above indicates clinically significant anxiety.[18] A validated simplified Chinese version of the HADS was used in this study. Multiple studies have confirmed its good reliability, validity, and internal consistency across various Chinese medical populations.[19–21] The EORTC QLQ-C30 is a widely used cancer-specific QOL instrument in international oncology research, which includes 30 items covering 15 domains, including 5 functional subscales (physical, role, emotional, social, and cognitive functions), 3 symptom subscales (fatigue, pain, and nausea/vomiting), 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties), and 1 global health status subscale.[22] A validated simplified Chinese version of the EORTC QLQ-C30 was also used in this study, which has demonstrated good reliability, validity, and consistency, and can be used for quality of life assessment in Chinese cancer patients.[23]

2.4 Study outcomes

The primary outcome was the longitudinal trajectory of anxiety scores among patients during AS. Secondary outcomes included: (1) long-term QOL scores among different subgroups; (2) incidence of non-progression-related conversion surgery across subgroups (with conversion classified as disease-progression–related when surgical indications were met, and as non-disease-progression–related otherwise); and (3) development, validation and performance evaluation of a classification model based on baseline characteristics and early follow-up data.

2.5 Statistical analyses

All statistical analyses were performed using R software (version 4.4.3) and GraphPad Prism version 9.1.1. Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and as median and interquartile range (IQR) for non-normally distributed data. Pearson's chi-square test was used to compare categorical variables. For continuous variables, Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used for non-normal distributions. All p-values were two-sided, and a p-value < 0.05 was considered statistically significant.

Anxiety trajectories were identified using a latent class mixed-effects growth model (R package: lcmm), with HADS-A scores as the dependent variable and follow-up months as the time variable. Models with

one to four latent classes were fitted sequentially. Model selection was based on minimizing Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) values, while ensuring that the sample size of each trajectory group was at least 5% of the total sample and had an average posterior probability (APP) greater than 0.70 within each group. The final model results were visualized with trajectory plots. Patients were assigned to groups according to their highest posterior probability, and after considering both clinical relevance and sample size, were further combined into two anxiety risk groups (high vs. low).

Longitudinal changes in EORTC QLQ-C30 QOL scores within and between anxiety risk groups were compared using mixed linear models. The cumulative incidence of conversion surgery for non-disease progression reasons among different anxiety risk groups was assessed using the Fine-Gray competing risk model, with “conversion surgery due to disease progression” defined as a competing event. For the development of the early identification model, anxiety risk group was used as the outcome variable. Baseline demographic and oncological characteristics, baseline HADS-A scores, and the change in HADS-A scores at 3–6 months (Δscore, calculated as the 3–6 month score minus the baseline score) were included as candidate predictors. Multicollinearity was assessed using the variance inflation factor (VIF), followed by variable selection and model construction through univariate and multivariate logistic regression analyses. A classification model was subsequently developed and visualized as a nomogram. Model performance was assessed by the area under the receiver operating characteristic curve (AUC) and compared with two reference models, a model incorporating baseline HADS-A score alone and a cutoff rule based on baseline HADS-A ≥ 8, using the DeLong test. The optimal probability threshold was determined by the Youden index, and the corresponding sensitivity, specificity, positive predictive value, and negative predictive value were reported. Incremental improvements in classification performance were evaluated using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. Internal validation was performed using bootstrap resampling, with the optimism-corrected AUC and calibration curve reported. Decision curve analysis (DCA) was conducted to evaluate the net clinical benefit of the model.

3. Results

3.1 Baseline characteristics

A total of 663 patients were included in the final analysis, with a median follow-up duration of 32.6 (18.1, 49.5) months. The mean age of the cohort was 41.7 ± 11.6 years, and 75.4% were female. Overall, 26.4% had undergone FNAB prior to enrollment, among whom 80.0% had a cytological diagnosis of suspicious for malignancy or malignant (Bethesda V-VI). 80.8% had a college degree or higher, and 84.2% were married. The mean tumor size was 0.6 ± 0.2 cm. The mean baseline HADS-A score was 3.9 ± 3.1, with 12.7% of patients had a score ≥ 8, and 3.0% had a score ≥ 11. Further details are provided in Table 1.

Table 1
Baseline Characteristics of the Cohort

Characteristic	Included Cohort (n = 663)
Age at diagnosis (years), mean ± SD	41.7 ± 11.6
Female, n (%)	500 (75.4)
BMI (kg/m^2), mean ± SD	23.5 ± 3.4
FNAB, n (%)	175 (26.4%)
Malignant	100 (57.1)
Suspicious for malignancy	40 (22.9)
AUS/FLUS	31 (17.7)
Nondiagnostic or unsatisfactory	4 (2.3)
Follow-up duration (months), median (IQR)	32.6 (18.1, 49.5)
Education level, n (%)	
Middle school or below	46 (6.9)
High school/technical school	69 (10.3)
College/university	384 (57.9)
Postgraduate or above	152 (22.9)
Unknown	12 (1.8)
Marital status, n (%)	
Married	558 (84.2)
Single/divorced	93 (14.0)
Unknown	12 (1.8)
Monthly income (CNY), n (%)	
≤3,000	32 (4.8)
3,000–5,000	88 (13.3)
5,000–10,000	170 (25.6)

SD, standard deviation; *BMI*, body mass index; *FNAB*, fine-needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance/follicular lesion of undetermined significance; *IQR*, interquartile range; *CNY*, Chinese yuan (1 CNY ≈ 0.15 USD); *TSH*, thyroid-stimulating hormone; *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety subscale.

* According to patient report or physician diagnosis: hypertension, diabetes, dyslipidemia, coronary artery disease, chronic lung disease, chronic kidney disease, skin disease, and malignant tumor.

Characteristic	Included Cohort (n = 663)
10,000–30,000	230 (34.7)
≥ 30,000	131 (19.8)
Unknown	12 (1.8)
Comorbidities, n (%) *	
None	464 (70.0)
≥1	199 (30.0)
Tumor size (cm), mean ± SD	0.6 ± 0.2
TSH (μIU/ml) (reference: 0.380–4.340)	1.8 (1.3, 2.5)
Baseline HADS-A score, mean ± SD	3.9 ± 3.1
Score ≥ 8, n (%)	84 (12.7)
Score ≥ 8, mean ± SD	9.6 ± 1.6
Score ≥ 11, n (%)	20 (3.0)
Score ≥ 11, mean ± SD	12.0 ± 1.2

SD, standard deviation; *BMI*, body mass index; *FNAB*, fine-needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance/follicular lesion of undetermined significance; *IQR*, interquartile range; *CNY*, Chinese yuan (1 CNY ≈ 0.15 USD); *TSH*, thyroid-stimulating hormone; *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety subscale.

* According to patient report or physician diagnosis: hypertension, diabetes, dyslipidemia, coronary artery disease, chronic lung disease, chronic kidney disease, skin disease, and malignant tumor.

3.2 Trajectories of HADS-A scores

Based on the optimal trajectory classification of HADS-A scores, patients were divided into four anxiety groups: persistently high (n = 112, 16.9%), worsening (n = 36, 5.4%), improving (n = 34, 5.1%), and persistently low (n = 481, 72.6%) (Fig. 2; model fit statistics are presented in Supplementary Tables 2 and 3). At baseline, anxiety scores of the improving group were comparable to that of the persistently high group (8.6 ± 1.6 vs 8.1 ± 2.2, $p > 0.05$), but gradually decreased over time and showed no significant difference to that of the persistently low group by month 18 (3.0 ± 2.0 vs 2.2 ± 1.9, $p > 0.05$), and sustained through month 36. Conversely, the baseline scores of the worsening group is comparable to that of the persistently low group (3.1 ± 2.0 vs 2.6 ± 2.0, $p > 0.05$), but gradually increased and were similar to that of the persistently high group by month 18 (7.0 ± 1.9 vs 8.2 ± 2.2, $p > 0.05$), and sustained through month 36. The HADS-A scores and the proportion of patients with scores ≥ 8 at each time point are shown in Supplementary Tables 4 and 5. There were no significant differences among the four groups in terms of age, sex, BMI, FNAB, FNAB results, education level, monthly income, marital status, tumor size, or TSH levels (Supplementary Table 6).

The persistently high and worsening groups were combined as the high anxiety risk group, while the persistently low and improving groups were categorized as the low anxiety risk group. There were no significant differences in baseline clinical characteristics of the two groups (Table 2). The high anxiety risk group had higher mean anxiety scores at baseline (6.9 ± 3.0 vs 3.0 ± 2.5, $p < 0.001$), as well as a higher proportion of patients with scores ≥ 8 (39.2% vs 5.0%, $p < 0.001$) and ≥ 11 (10.1% vs 1.0%, $p < 0.001$) compared to the low-risk group. These differences remained significant at months 36; with the high-risk group maintaining higher mean anxiety scores (7.2 ± 2.3 vs 2.3 ± 2.1, $p < 0.001$), and greater proportion of patients with scores ≥ 8 (39.7% vs 0.7%, $p < 0.001$) and ≥ 11 (10.3% vs 0.4%, $p < 0.001$).

Table 2
Baseline clinical characteristics of patients in different anxiety risk groups

Characteristics	High anxiety risk group	Low anxiety risk group	p value
	n = 148 (22.3%)	n = 515 (77.7%)	
Age (y)	40.9 ± 11.7	41.9 ± 11.6	0.284
Female	116 (78.4)	384 (74.6)	0.400
BMI (kg/m^2)	23.4 ± 3.6	23.6 ± 3.4	0.405
FNAB, n (%)	115 (77.7)	142 (27.6)	0.239
Malignant	20 (60.6)	80 (56.3)	0.631
Suspicious for malignancy	9 (27.3)	31 (21.8)	
AUS/FLUS	3 (9.1)	28 (19.8)	
Nondiagnostic or unsatisfactory	1 (3.0)	3 (2.1)	
Education level			0.657
Middle school or below	9 (6.1)	37 (7.2)	
High/technical school	19 (12.8)	50 (9.7)	
College/university	85 (57.4)	299 (58.1)	
Postgraduate or above	31 (20.9)	121 (23.5)	
Unknown	4 (2.7)	8 (1.6)	
Marital status			0.802
Married	122 (82.4)	436 (84.7)	
Single/divorced	22 (14.9)	71 (13.8)	
Unknown	4 (2.7)	8 (1.6)	
Monthly income (CNY)			0.359
≤3,000	9 (6.1)	23 (4.5)	
3,000–5,000	25 (16.9)	63 (12.2)	

SD, standard deviation; *BMI*, body mass index; *FNAB*, fine-needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance/follicular lesion of undetermined significance; *IQR*, interquartile range; *CNY*, Chinese yuan (1 CNY ≈ 0.15 USD); *TSH*, thyroid-stimulating hormone; *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety subscale.

* According to patient report or physician diagnosis: hypertension, diabetes, dyslipidemia, coronary artery disease, chronic lung disease, chronic kidney disease, skin disease, and malignant tumor.

Characteristics	High anxiety risk group	Low anxiety risk group	p value
	n = 148 (22.3%)	n = 515 (77.7%)	
5,000–10,000	36 (24.3)	134 (26.0)	
10,000–30,000	51 (34.5)	179 (34.8)	
≥ 30,000	23 (15.5)	108 (21.0)	
Unknown	4 (2.7)	8 (1.6)	
Comorbidities*			0.851
None	105 (70.9)	359 (69.7)	
≥1	43 (29.1)	156 (30.3)	
Tumor size (cm)	0.57 ± 0.20	0.6 ± 0.2	0.589
TSH (μIU/ml)	2.12 ± 1.46	1.8 (1.3, 2.4)	0.990
Baseline HADS-A score	6.90 ± 3.04	3.0 ± 2.5	< 0.001
≥ 8, n (%)	58 (39.2)	26 (5.0)	< 0.001
≥ 8, mean ± SD	9.76 ± 1.76	9.2 ± 1.2	0.171
≥ 11, n (%)	15 (10.1)	5 (1.0)	< 0.001
≥ 11, mean ± SD	12.27 ± 1.22	11.2 ± 0.5	0.076

SD, standard deviation; *BMI*, body mass index; *FNAB*, fine-needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance/follicular lesion of undetermined significance; *IQR*, interquartile range; *CNY*, Chinese yuan (1 CNY ≈ 0.15 USD); *TSH*, thyroid-stimulating hormone; *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety subscale.

* According to patient report or physician diagnosis: hypertension, diabetes, dyslipidemia, coronary artery disease, chronic lung disease, chronic kidney disease, skin disease, and malignant tumor.

3.3 Mixed-effects linear model analysis of QOL

The QOL scores of the four anxiety trajectory groups showed patterns similar to those of their HADS-A scores throughout the follow-up period (Supplementary Fig. 1). The persistently high-anxiety group had significantly worse scores than the persistently low-anxiety group in all 15 domains throughout follow-up (all $p < 0.05$). The improving group showed gradual improvement in QOL scores over time, with most domains eventually reaching levels comparable to those of the persistently low group, whereas the worsening group showed gradual deterioration over time, with most domains eventually reaching levels similar to those of the persistently high group.

Mixed-effects linear model analyses showed that high anxiety risk group had significantly worse QOL scores than the low anxiety risk group across all 15 domains of the EORTC QLQ-C30 (all $p < 0.001$; Fig. 3,

Supplementary Table 7), especially emotional functioning (estimate: 25.7), insomnia (estimate: -24.2), cognitive functioning (estimate: 20.6), fatigue (estimate: -19.7), and global health status (estimate: 16.4). In both groups, most QOL domains either improved significantly or remained stable over time, whereas a few domains such as role functioning worsened significantly in both groups (all $p < 0.05$).

3.4 Competing risk analysis of non-progression-related conversion surgery

In this cohort, 49 of 663 patients (7.4%) converted from AS to surgery. The overall conversion rate showed no significant difference between the high anxiety risk and low anxiety risk groups (8.1% vs 7.2%, $p = 0.722$; Supplementary Table 8). Notably, among patients underwent conversion surgery, the proportion of non-progression-related conversion surgery was higher in the high anxiety risk group than in the low anxiety risk group (75.0% vs 40.5%), with the difference reaching marginal significance ($p = 0.051$; Supplementary Table 8). Competing risk analysis showed that the cumulative incidence of non-progression-related conversion surgery in the high anxiety risk group was 3.6%, 7.0%, and 7.0% at 12, 24, and 36 months of follow-up respectively, compared with 0.8%, 2.7%, and 3.7% in the low anxiety risk group, with the difference likewise reaching marginal significance (Gray's test, $p = 0.068$; Fig. 4, Supplementary Table 9).

3.5 Development and validation of the clinical prediction model

Among the 520 patients who completed the 3–6 month HADS-A follow-up assessment, only baseline HADS-A scores (6.7 ± 3.0 vs 3.0 ± 2.5, $p < 0.001$) and the change in scores from baseline to 3–6 months (Δscore: 0.8 ± 2.6 vs -0.5 ± 2.3, $p < 0.001$) showed significant differences between the two groups. In univariate logistic regression analysis, only baseline HADS-A score (OR = 1.603, 95% CI: 1.464–1.771, $p < 0.001$) and Δscore (OR = 1.277, 95% CI: 1.164–1.409, $p < 0.001$) were significantly associated with high anxiety risk, whereas demographic and oncological variables (age, sex, BMI, FNAB, tumor size, income, marital status, and education level) did not reach statistical significance (all $p > 0.05$). Based on clinical relevance, all 10 variables were included in the multivariate logistic regression analysis. No significant multicollinearity was found among the candidate variables (maximum VIF = 2.14, all < 5). Multivariate analysis showed that only baseline HADS-A score (OR = 2.366, 95% CI: 2.019–2.842, $p < 0.001$) and Δscore (OR = 2.123, 95% CI: 1.794–2.573, $p < 0.001$) were independent factors associated with high anxiety risk (Table 3). Therefore, only baseline HADS-A score and Δscore were included in the final model, which was visualized with a nomogram (Fig. 5).

Table 3
Results of multivariate logistic regression analysis of factors associated with the high-risk anxiety group

Variable	β	OR(95%CI)	p value
Age	-0.003	0.997(0.964–1.030)	0.865
Sex [Female]	0.054	1.055(0.476–2.416)	0.896
BMI	-0.023	0.977(0.870–1.096)	0.694
FNAB [Yes]	-0.040	0.961(0.453–1.998)	0.916
Education [College or above])	-0.226	0.798(0.316–2.021)	0.632
Marital status [Married]	-0.032	0.968(0.375–2.406)	0.945
Monthly income [≥ 10,000 CNY]	0.181	1.198(0.598–2.431)	0.612
Tumor size	-1.070	0.343(0.070–1.361)	0.151
Baseline HADS-A score	0.861	2.366(2.019–2.842)	< 0.001
Δ score	0.753	2.123(1.794–2.573)	< 0.001

β, regression coefficient; *OR*, odds ratio; *CI*, confidence interval; *BMI*, body mass index; *FNAB*, fine-needle aspiration biopsy; *CNY*, Chinese yuan (1 CNY ≈ 0.15 USD); *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety subscale.

The final model achieved an AUC of 0.924 (95% CI: 0.895–0.953), and DeLong's test showed that its discriminative ability was significantly superior to that of the baseline HADS-A score-only model (AUC = 0.829, p < 0.001) and the baseline HADS-A ≥ 8 cutoff rule (AUC = 0.662, p < 0.001) (Fig. 6A). At the optimal Youden cutoff (P = 0.277), the model had a sensitivity of 83.2%, specificity of 88.5%, positive predictive value of 66.7%, and negative predictive value of 95.0%. Bootstrap internal validation yielded a corrected AUC of 0.923, and the calibration curve showed good agreement between predicted and observed probabilities (Fig. 6B).

Compared with the baseline-only model, the final model had an integrated discrimination improvement (IDI) of 0.256 (p < 0.001), with the mean predicted probability increasing by 0.200 in the high anxiety risk group and decreasing by 0.056 in the low anxiety risk group. At the optimal threshold (P = 0.277), the categorical net reclassification improvement (NRI) was 0.183 (p < 0.001), with a net 12.4% of patients in the high anxiety risk group (NRI + = 0.124) and a net 5.9% of patients in the low anxiety risk group (NRI−=0.059) being correctly reclassified (Supplementary Table 10).

Decision curve analysis (DCA) showed that across thresholds of 0.05 to 0.95, net benefit gradually decreased with increasing thresholds but remained superior to “treat all” or “treat none” strategies (Fig. 6C, Supplementary Table 11).

4. Discussion

Anxiety is a common but poorly characterized challenge during AS for low-risk PTC patients. In this real-world prospective cohort study, we applied latent class mixed growth model to this population for the first time and successfully identified four distinct anxiety trajectories over a median follow-up of 32.6 months. Approximately 22.3% of patients were classified as high anxiety risk, characterized by persistently high or worsening anxiety, and had significantly worse QOL and a trend toward higher non-progression-related conversion surgery rates. The classification model, based on baseline HADS-A scores and their changes at 3-6months, demonstrated excellent discriminative performance (AUC 0.924), significantly outperforming both the baseline-only model and the HADS-A ≥ 8 cutoff rule, and showed substantial net clinical benefit, providing a practical tool for the early identification of high anxiety risk patients.

Trajectory analysis revealed substantial heterogeneity in the dynamic changes of anxiety among the AS population over the 3-year follow-up period. Most patients (77.7%) maintained persistently low or gradually improving anxiety throughout follow-up, consistent with prior reports suggesting that AS does not systematically impair psychological well-being.[24,25] However, 16.9% of patients exhibited persistently high anxiety, and 5.4% experienced a progressive increase, gradually reaching levels comparable to the persistently high group and remaining so throughout the follow-up. Consistent with our findings, a large U.S. cohort study based on the U.S. National Health and Aging Trends Study (NHATS) involving 1766 elderly cancer survivors also identified four similar distinct trajectories of anxiety and depression using the Patient Health Questionnaire-4 (PHQ-4), suggesting that cancer-related psychological burden may follow a similar heterogeneous distribution.[26] Notably, although previous studies have suggested associations between anxiety and factors such as female gender, younger age, or larger tumor size in thyroid cancer patients,[27–29] we did not observe significant demographic or oncological differences between the high anxiety risk and low anxiety risk groups. This suggests that conventional clinical characteristics may be insufficient for effectively identifying high anxiety risk patients within the AS population, highlighting the need for repeated, standardized and quantitative assessment tools to enable the early identification of these patients.

Different anxiety status may also influence long-term QOL and treatment decision-making. Numerous studies have demonstrated that anxiety exerts a significant negative impact on the QOL of cancer patients.[30–32] In a study involving 205 breast cancer patients, anxiety had a significantly direct negative effect on QOL scores ($b = -1.233$, $t = -4.188$, $p < 0.001$).[33] In our study, linear mixed-effects model analysis showed that high anxiety risk patients had significantly worse QOL scores across all 15 EORTC QLQ-C30 domains throughout the follow-up period compared to the low anxiety risk group (all $p < 0.001$), with this difference extending to domains seemingly unrelated to low-risk suspicious malignant thyroid nodules themselves, such as pain, nausea and vomiting, and constipation. In fact, this broad-spectrum impairment is consistent with the well-established somatization effects of chronic anxiety, whereby patients' perception of physical discomfort is amplified under anxious states.[34] Furthermore, QoL analysis across the four trajectory groups revealed a notable convergence pattern over time similar to those of the anxiety trajectories, suggesting a close dynamic association between QOL and anxiety, and

that sustained anxiety may progressively impair broader dimensions of patients' health. Nevertheless, we acknowledge that unmeasured confounding factors, such as personality traits, may have partly contributed to this pattern. Future studies incorporating personality assessments is needed to clarify this relationship.

With regard to changes in treatment decisions, the overall conversion rate from AS to surgery was 7.4% in our cohort, comparable to 8.4% (242/2896, median follow-up 8.4 years) reported by Fujishima et al. at Kuma Hospital in Japan.[35] However, the proportion of non-progression-related conversion surgery has varied widely across studies, ranging from 29.1% (16/550, median follow-up 40.3 months) reported by Levyn et al.[36] to 43.2% (37/155, median follow-up 71 months) reported by Sawka et al.[37] to 70.2% reported by Fujishima et al.[35] In our cohort, 49.0% of conversions were non-progression-related, despite standardized shared decision-making and thorough communication throughout follow-up, suggesting factors beyond information deficit such as anxiety may have driven these conversions. Our results show that the cumulative incidence of non-progression-related conversion surgery was higher in the high anxiety risk group than in the low anxiety risk group (75.0% vs 40.5%), with the difference reaching marginal significance ($p = 0.051$). Competing risk analysis likewise revealed that the cumulative incidence of non-progression-related conversion surgery was consistently higher in the high anxiety risk group across all time points, with the difference again reaching marginal significance ($p = 0.068$), possibly due to the limited sample size and follow-up duration. Nonetheless, these findings suggest that anxiety may contribute to non-progression-related conversion surgery but is unlikely to be the sole reason. Previous studies have identified multiple other factors that may influence treatment decisions during AS, including family responsibilities, coping styles, personal preferences.[8,11,37–38] However, how patients weigh and prioritize these competing factors in shaping their treatment decisions warrant further investigation.

While the psychological health of AS patients has received increasing attention, the clinical value of psychological interventions in this population remains unclear. To date, no systematic evaluation has been conducted to identify patients who might benefit from psychological support, or to determine the mode, outcomes, and efficacy of such interventions. This may be partly due to the perception that AS patients have relatively mild disease, and that psychological distress may resolve over time without additional support.[38–40] However, our findings challenge this assumption. Nearly one-quarter of patients remained at high anxiety risk throughout the follow-up period, and had significantly higher anxiety scores at both baseline and month 36 compared to the low anxiety risk group. Further analysis showed that, while 39.2% of the high anxiety risk patients met the criteria for possible anxiety and 10.1% met the diagnostic threshold for anxiety at baseline, these percentages remained largely unchanged till the third year of follow-up (39.7% and 10.3% respectively). These results suggest that a substantial proportion of AS patients experience persistent psychological distress, which is unlikely to resolve spontaneously without effective intervention. Therefore, these patients should be prioritized for attention and psychological intervention, as they are at greatest risk for sustained psychological distress during AS.

It is important to note that while the overall proportion of patients with possible or diagnosed anxiety is relatively low, the absolute number of affected individuals is considerable given the substantial patient base. With the recent published 2025 ATA guidelines explicitly recommending AS for low-risk PTC,[6] the number of patients managed with AS and experience psychological distress is expected to increase further, making this issue increasingly important. However, in the current era of precision treatment, implementing psychological interventions for all patients would significantly increase clinical workload and hinder effective delivery of these interventions, likely resulting in inefficient use of healthcare resources. Therefore, it is crucial to identify those in true need. Given the typical six-month follow-up interval for AS, we developed a clinical classification tool for identifying high anxiety risk patients based on baseline HADS-A scores and changes at 3–6 months (Δscore). The results showed that both were independent factors associated with high anxiety risk (both $p < 0.001$), and the resulting classification model demonstrated excellent performance (AUC = 0.924), significantly outperforming both the baseline HADS-A score-only model (AUC = 0.829, $p < 0.001$) and the baseline HADS-A ≥ 8 cutoff rule (AUC = 0.662, $p < 0.001$). Notably, approximately 10.5% of patients whose anxiety trajectories shift during early follow-up (improving and worsening group). Our model, by incorporating just two early assessments, enables timely identification of these patients and reliably distinguishes worsening from improving patients. The IDI (0.256, $p < 0.001$) and NRI (0.183, $p < 0.001$) further confirmed that the inclusion of Δ score substantially enhanced the separation of predicted probabilities between the high and low anxiety risk groups and achieved effective reclassification of patients at the optimal threshold, thereby providing tangible incremental predictive value over baseline-only assessment. Furthermore, DCA indicated that, compared with “treat all” or “treat none” strategies, model-guided targeted interventions can effectively reduce unnecessary use of clinical resources and also minimize the chances of missing high anxiety risk patients who require intervention, thus maximizing clinical benefit.

A notable feature of the present study is the inclusion of patients enrolled based on highly suspicious ultrasound features without prior cytological confirmation, which differs from most previous AS studies. In this study, 73.6% of patients had not undergone FNAB. In fact, although acceptance of FNAB among Chinese patients has been gradually improving, it remains limited overall, and the clinical diagnosis of thyroid cancer in China still relies predominantly on ultrasonography. Post hoc analysis revealed no significant differences between patients with and without FNAB in baseline anxiety scores ($p = 0.269$) or any EORTC QLQ-C30 domain (all $p > 0.05$) (Supplementary Table 12). Among patients who underwent FNAB, no significant differences were observed between those diagnosed as Bethesda V-VI and those classified as Bethesda I-IV (Supplementary Table 13), consistent with our previous findings.[25] Furthermore, the proportion of patients who had undergone FNAB did not differ between the high and low anxiety risk groups ($p = 0.239$). These findings suggest that FNAB status did not affect patients’ psychological or quality of life outcomes, possibly due to the standardized clinical disclosure procedures in our study established a comparable level of risk perception regardless of FNAB status in our study.

This study is the first to identify the long-term dynamic anxiety trajectories of patients undergoing AS for highly suspicious thyroid malignant nodules ≤1cm using real-world prospective data, and to develop a

classification model for identifying high anxiety risk patients based on early follow-up data. These findings provide a strong theoretical and practical support for the comprehensive management and clinical implementation of targeted psychological interventions during AS. Prioritizing high anxiety risk patients for targeted psychological support may not only improve their QOL but also potentially reduce non-progression-related conversion surgeries, thereby preserving the intended benefits of AS.

Several limitations of this study should be acknowledged. The study was conducted at a single center in China, cultural factors may influence anxiety expression and attitudes toward AS, limiting generalizability. Additionally, the sample size and follow-up duration were limited. Larger multicenter cohorts and longer follow-up periods are needed to better characterize long-term anxiety trajectories and associated factors in AS patients. Moreover, this study focused on anxiety assessed by HADS-A as the core outcome and did not systematically collect data on individual-level sources of anxiety or other important psychological dimensions that patients may experience during AS, such as fear of cancer progression or recurrence, illness uncertainty, decision regret, family pressure, and social support, thereby precluding further elucidation of the psychological mechanisms underlying the different anxiety trajectories. Future research exploring patient-reported drivers of anxiety would provide complementary insights and inform the design of targeted interventions.

5. Conclusions

The anxiety status was highly heterogeneous among patients with ≤1cm highly suspicious thyroid nodules under AS. Approximately one-quarter of patients exhibited persistently high or worsening anxiety, and had significantly poorer QOL and may be more likely to convert to surgery due to non-progression-related reasons during follow-up. The classification tool developed using baseline HADS-A scores and 3–6 months score changes enable early and accurate identification of high anxiety risk patients, providing a foundation for precision psychological interventions in clinical practice.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Review Committee of PUMCH (ethics approval number: JS-2454). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (as revised in 2013). The study was also registered in the National Medical Research Registration Information System of China (registration number: MR-11-23-034312). Written informed consent was obtained from all individual participants prior to enrollment.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the informed consent agreement approved by the Ethics Review Committee of Peking Union Medical College Hospital, but are available from the corresponding author on reasonable request.

Competing interests

Author 1: Zifeng Kuang: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 2: Chenjia Zhang: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 3: Hao Zhao: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 4: Ya Zhao: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 5: Hua Huang: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 6: Guannan Ge: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 7: Yue Cao: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 8: Yu Xia: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 9: Bei Yang: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 10: Yajun Zhang: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 11: Jingjing Yao: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author 12: Xiaoyi Li: Declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Author 1: Zifeng Kuang: Conceptualization (supporting); Methodology (lead); Writing - original draft (lead); Writing - review and editing (equal); Formal analysis (lead). Author 2: Chenjia Zhang: Methodology (supporting). Author 3: Hao Zhao: Formal analysis (supporting); Writing - review and editing (supporting). Author 4: Ya Zhao: Data curation (lead). Author 5: Hua Huang: Conceptualization (supporting). Author 6: Guannan Ge: Conceptualization (supporting); Writing - review and editing (supporting). Author 7: Yue Cao: Data curation (supporting); Methodology (supporting). Author 8: Yu Xia: Data curation (supporting). Author 9: Bei Yang: Data curation (supporting). Author 10: Yajun Zhang: Data curation (supporting). Author 11: Jingjing Yao: Data curation (supporting). Author 12: Xiaoyi Li: Conceptualization (lead); Methodology (supporting); Writing - review and editing (equal); Supervision (lead).

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Figures

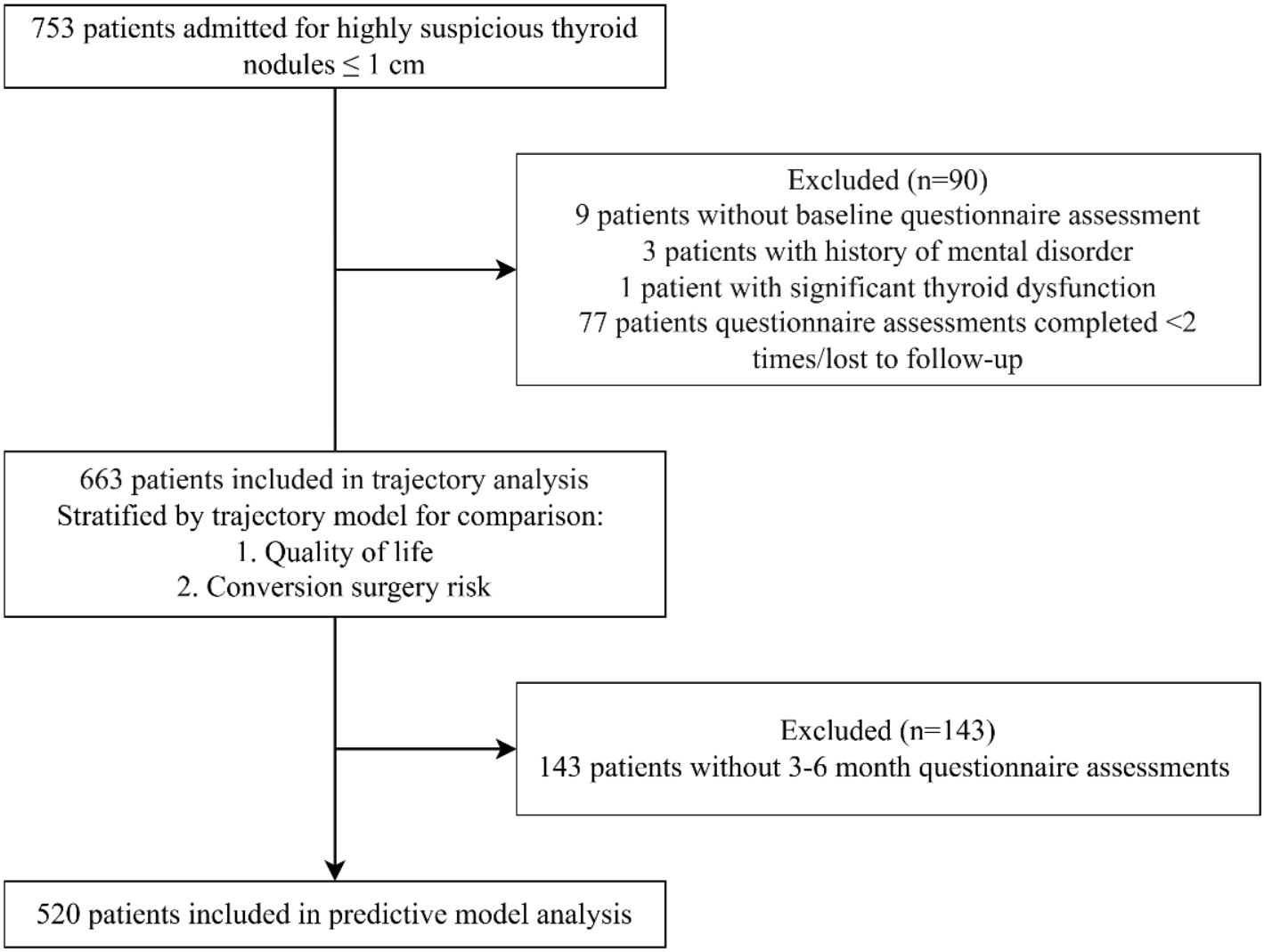


Figure 1

Study flow chart

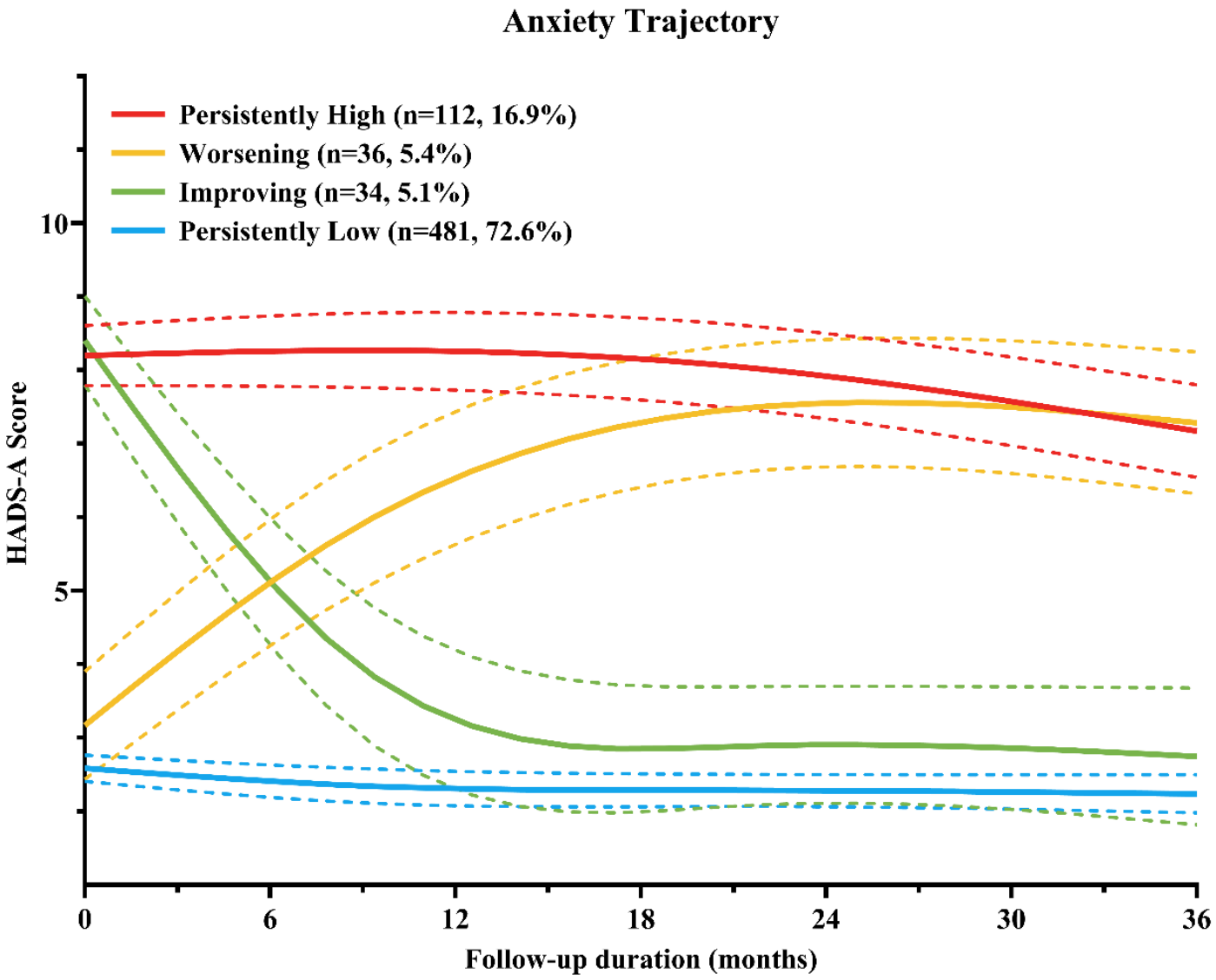


Figure 2

Longitudinal Trajectories of HADS-A Scores Across Different Groups

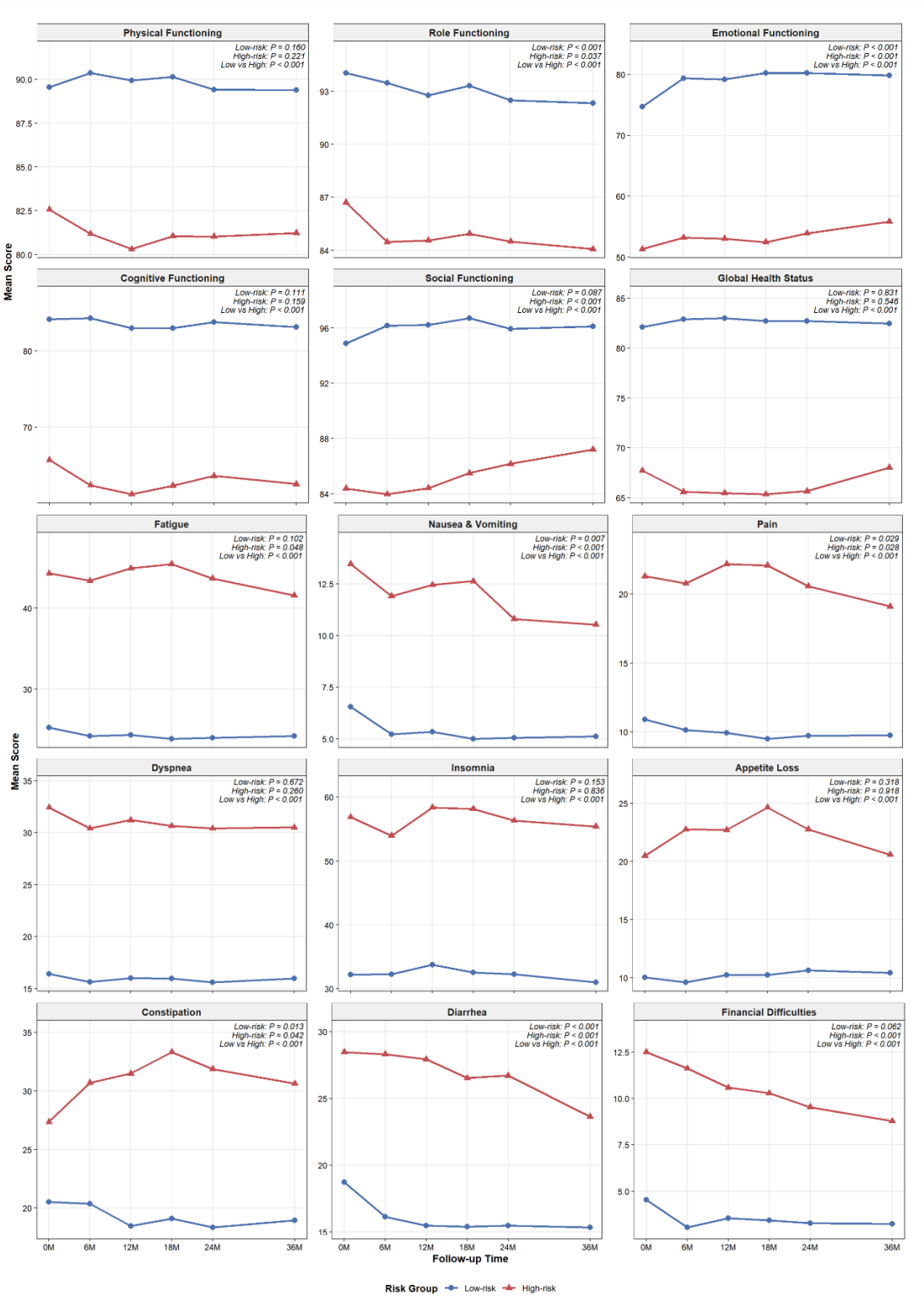


Figure 3

Mixed linear model analysis of EORTC QLQ-C30 questionnaire between high risk and low risk patients. "Low vs High" refers to the between-group comparison results between the low anxiety risk group and the high anxiety risk group.

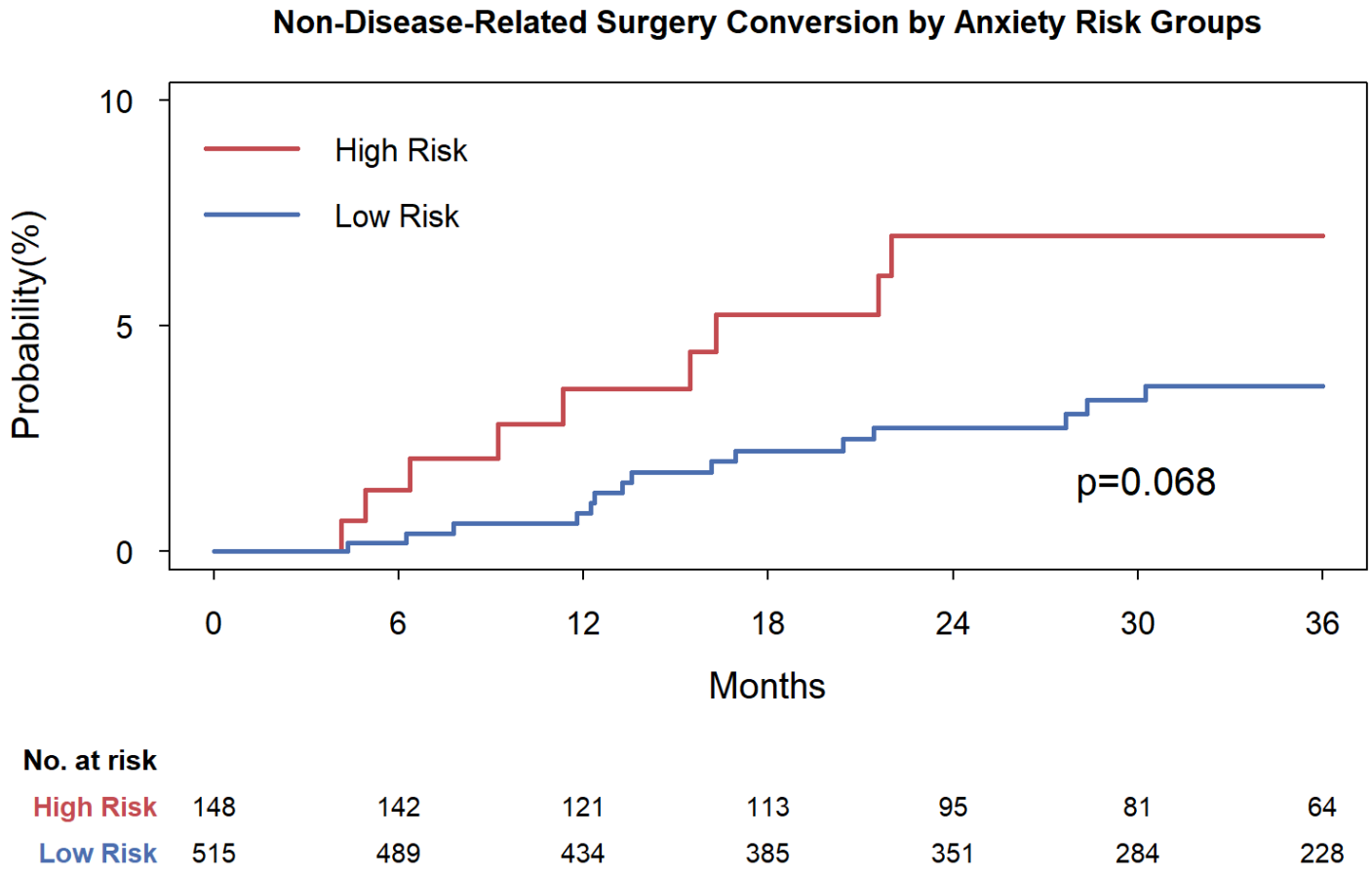


Figure 4

Cumulative Incidence of Non–Disease Progression–Related Conversion Surgery by Anxiety Risk Groups.

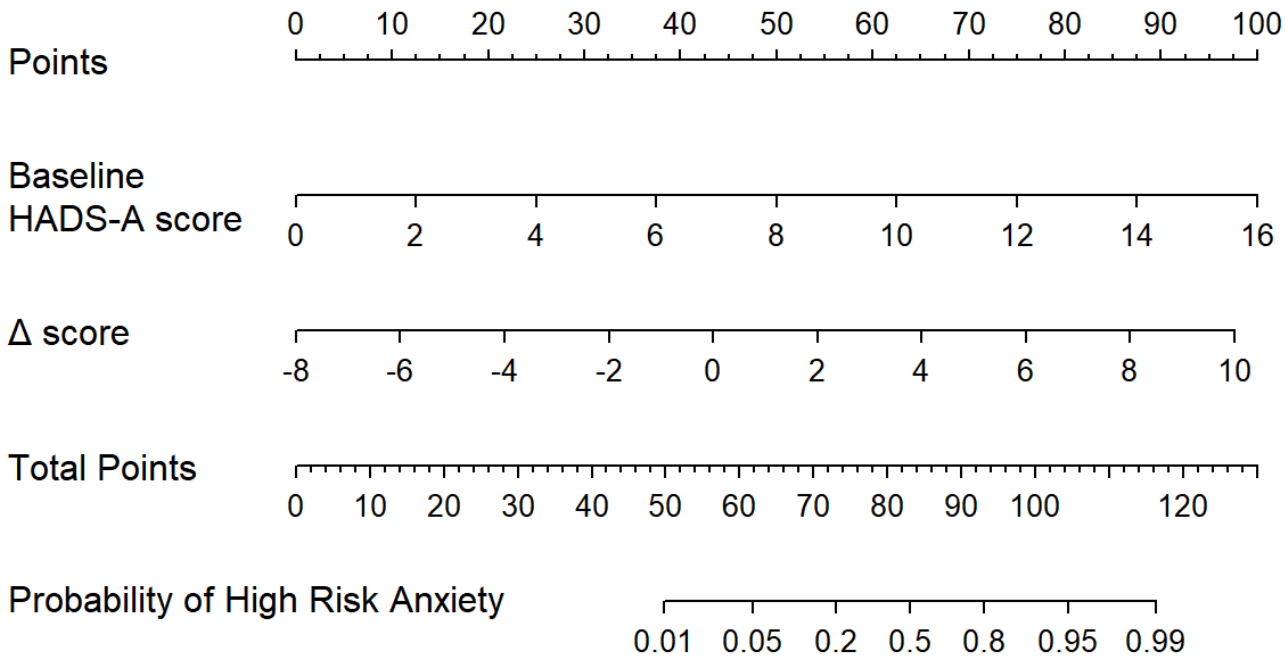


Figure 5

Nomogram of the predictive model for high anxiety risk patients based on baseline HADS-A score and Δ score

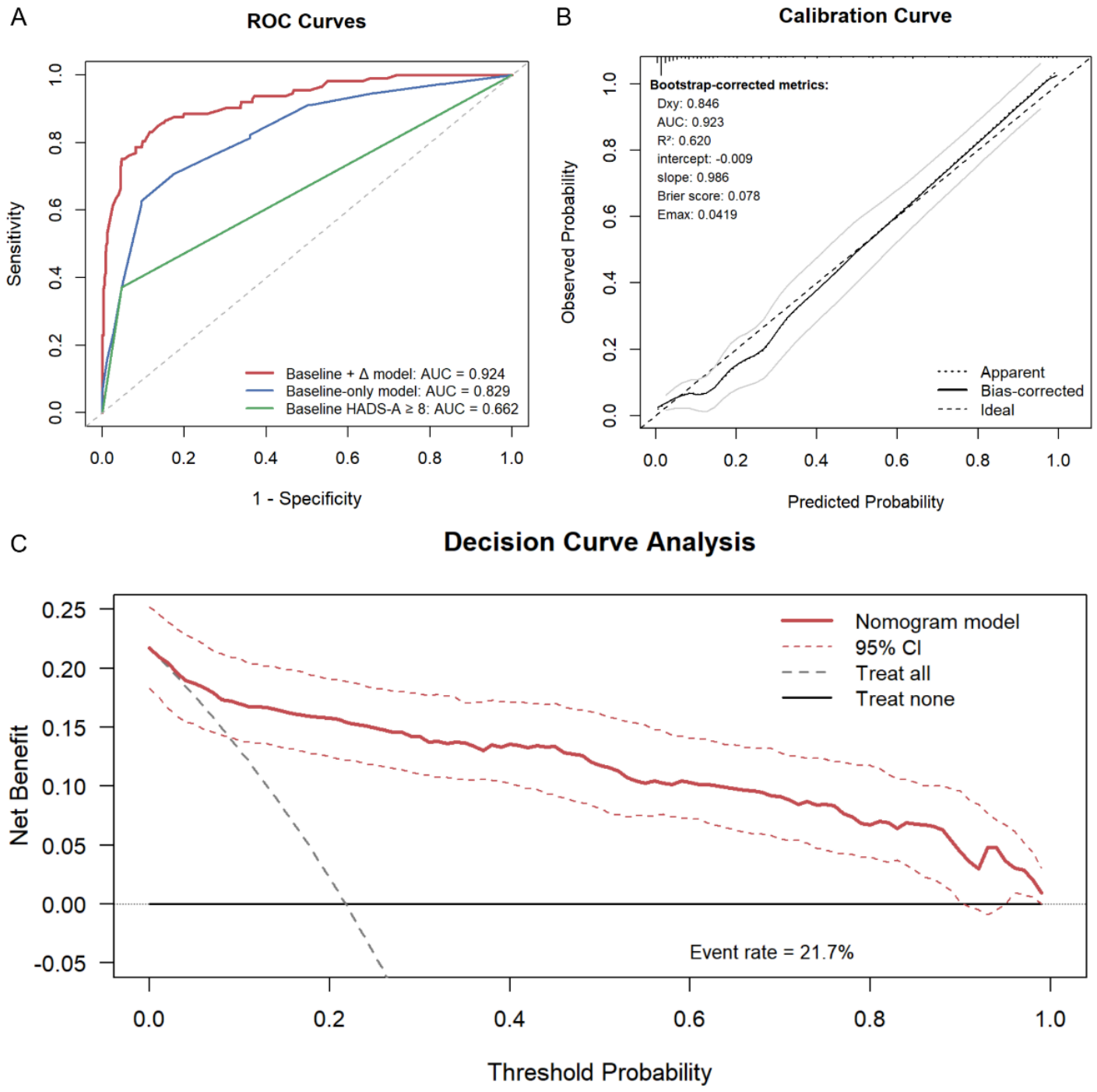


Figure 6

Comprehensive Evaluation Results of the Nomogram Prediction Model. A: ROC Curve; B: Calibration Curve; C: Decision Curve Analysis

Supplementary Files

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