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Li Zhang
Tianjin Medical University Cancer Institute and Hospital
Fan Sun
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
Yansheng Wu
Tianjin Medical University Cancer Institute and Hospital
Lijuan Wei
Tianjin Medical University Cancer Institute and Hospital
Hailing Ren
Tianjin Medical University Cancer Institute and Hospital
Qingjuan Yao
Tianjin Medical University General Hospital
Fanming Kong
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
Jing Zhang
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
Jie Hao
The First Affiliated Hospital of Nankai University
Yu Sun
Second Hospital of Tianjin Medical University
Rui Feng
Tianjin Central Hospital of Gynecology Obstetrics
Rende Guo
Tianjin First Center Hospital
Lijun Chen
Tianjin Binhai New District Dagang Hospital
Yuqi Han
Tianjin Medical University Cancer Institute and Hospital

Yehui Shi

shiyehui@tjmuch.com

Tianjin Medical University Cancer Institute and Hospital

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Impact of an Artificial Intelligence Management Model on Psychological and Behavioral Outcomes in Breast Cancer Patients Receiving Home-based CDK4/6i Therapy: A Multicenter Randomized Controlled Trial

Li Zhang[1], Fan Sun[2], Yansheng Wu[1], Lijuan Wei[1], Hailing Ren[1], Qingjuan Yao[3], Fanming Kong[2], Jing Zhang[2], Jie Hao[4], Yu Sun[5], Rui Feng[6], Rende Guo[7], Lijun Chen[8], Yuqi Han[1] and Yehui Shi[1]

1 Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

2 First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China

3 Tianjin Medical University General Hospital, Tianjin, China

4 The First Affiliated Hospital of Nankai University, Tianjin, China

5 Second Hospital of Tianjin Medical University, Tianjin, China

6 Tianjin Central Hospital of Gynecology Obstetrics, Tianjin, China

7 Tianjin First Center Hospital, Tianjin, China

8 Tianjin Binhai New District Dagang Hospital, TianJin, China

Correspondence: shiyehui@tjmuch.com (Yehui Shi)

Abstract:

Background:

Endocrine therapy combined with CDK4/6 inhibitors (CDK4/6i) is the preferred regimen for first-line and adjuvant treatment of HR+/HER2− breast cancer. Oral administration has shifted the primary setting of care to home environments. However, traditional care models rely heavily on episodic outpatient visits, failing to provide proactive, continuous, and personalized transitional care. This creates a "service gap," leading to psychological distress, compromised compliance, and delayed toxicity management during long-term out-of-hospital therapy. We aimed to evaluate the effects of an artificial intelligence (AI)-driven management model and a customized active follow-up model on psychological and behavioral outcomes in these patients.

Methods:

This multicenter randomized controlled trial dynamically evaluated patients using the Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), EORTC QLQ-C30, and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Findings:

Between 2024 and 2025, 189 patients receiving CDK4/6i across multiple hospitals in Tianjin were randomized. Critically, 161 patients completed the final analysis (AI-driven management: $n = 53$; customized active follow-up: $n = 54$; standard care: $n = 54$), with balanced baseline characteristics ($P > 0.05$). For the primary outcome, both the AI-driven and customized follow-up groups demonstrated significantly superior efficacy in maintaining anxiety stability and alleviating depression compared with standard care (both $P \leq 0.001$). In the standard care group, psychological states deteriorated significantly over time, with depression scores peaking at week 16 (T2). For secondary outcomes, both intervention groups showed significantly better cognitive, emotional, and social functioning, as well as global health status, than the standard care group (all $P < 0.05$). Multiple correspondence analysis revealed a robust positive intra-family covariation of negative emotions within patient-caregiver dyads, closely clustering with a fixed caregiver and comorbidities. SAS and SDS scores were positively correlated with fasting blood glucose and liver function indicators, notably alanine aminotransferase (ALT) (all $P < 0.05$). Furthermore, real-time AI monitoring yielded a higher PRO-CTCAE adverse event capture rate, mitigating the risk of high-grade toxicities.

Interpretation:

Both AI-driven and customized follow-up models significantly improve anxiety, depression, and quality of life in breast cancer patients on home-based CDK4/6i therapy. The AI model offers distinct scaling advantages in cognitive support and real-time toxicity monitoring, providing robust evidence for a holistic "bio-psycho-social" precision oncology home-management paradigm.

Clinical Trial Registration: NCT07409298||https://www.clinicaltrials.gov/(Registration date: February 12, 2026; First submitted: January 20, 2026)

Keywords: CDK4/6 inhibitors; Breast cancer; Artificial intelligence; Follow-up; Psychological intervention

Introduction:

Breast cancer remains the most prevalent malignancy among women globally, with a rising incidence observed in China. Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer is the most common subtype, accounting for approximately 65%–70% of all cases [1]. Endocrine therapy combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) is currently the preferred first-line standard of care for advanced HR+/HER2- breast cancer, and its application has recently expanded to the adjuvant setting for high-risk early-stage disease[2]. Several CDK4/6i agents, including ribociclib, palbociclib, abemaciclib, and dalpiciclib, have been approved in China. These agents delay disease progression by inhibiting cell cycle regulatory pathways and may offer additional clinical benefits, such as immunomodulation and overall survival (OS) prolongation[3]. However, emerging evidence suggests that these therapeutic regimens can trigger psychological distress, such as anxiety and depression, which significantly compromises patients' quality of life (QoL). Consequently, the integration of psychological interventions has become increasingly imperative [4].

The paradigm shift toward oral CDK4/6i therapy has transitioned the primary landscape of cancer management from clinical settings to home-based environments. This transition necessitates a novel management framework capable of transcending spatiotemporal constraints. Conventional follow-up, which relies on sporadic outpatient visits, often fails to provide proactive, continuous, and personalized support for home-based patients. This limitation results in a significant "service gap" in psychological well-being, behavioral compliance, and the self-management of adverse events (AEs). To bridge this gap, some medical centers have explored proactive strategies, such as establishing follow-up centers that offer "customized active follow-up" via telephone or text messaging[5]. While superior to routine care, this model is constrained by high labor costs and limited service hours, making it difficult to achieve 24/7 real-time responsiveness and deep personalization.

Advances in information technology, particularly artificial intelligence (AI), have introduced innovative avenues for psychological intervention [6]. AI-driven "virtual physicians" can evaluate patients based on psychological profiles and physiological indicators, facilitating early identification of emotional risks and the formulation of tailored intervention protocols[7,8]. Furthermore, AI can provide continuous emotional support across different treatment phases, provide early warnings for mood fluctuations, and optimize intervention content to enhance patient compliance and satisfaction [9].

The present study aims to evaluate the efficacy of an AI-driven management model in improving psychological and behavioral outcomes among patients undergoing home-based CDK4/6i therapy through a multicenter randomized controlled trial (RCT).

Methods:

Research Design

This study was designed as a prospective, open-label, parallel-group, multicenter randomized controlled trial (RCT). It aimed to evaluate the efficacy of three distinct management paradigms—an AI-driven management model (Group A), a customized proactive follow-up model (Group B), and routine educational follow-up (Group C)—in ameliorating anxiety, depression, and other behavioral outcomes among breast cancer patients receiving home-based CDK4/6 inhibitor (CDK4/6i) therapy. Participants were recruited from multiple cancer centers, including the Tianjin Medical University Cancer Institute and Hospital. All subjects were enrolled after providing written informed consent. Eligible participants were randomized in a 1:1:1 ratio into Group A, B, or C. The primary endpoints were the longitudinal changes in the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores. Secondary endpoints included changes in quality of life (QoL), patient-reported adverse events (PRO-AEs), and relevant serological biomarkers. To minimize the

impact of baseline imbalances, stratified randomization was employed, using baseline anxiety and depression levels (none vs. present) as stratification factors. This ensured comparability across the three arms regarding key confounding variables.

Recruitment and Selection Criteria

Participants were recruited using convenience sampling. The inclusion criteria were: (1) females aged ≥18 years, regardless of menopausal status; (2) histologically confirmed HR+/HER2- breast cancer (HER2-negative defined as IHC 0/1+ or IHC 2+ with negative FISH) receiving CDK4/6i therapy; (3) ECOG performance status of 0–2; (4) no history of severe psychiatric disorders (e.g., bipolar disorder, schizophrenia) and possession of adequate mental capacity to engage in psychological interventions; (5) concurrent participation in a rehabilitation program (e.g., exercise or physical therapy); (6) provision of written informed consent; and (7) proficiency in digital operations via smartphone or computer for questionnaire completion and interaction with the virtual physician. The exclusion criteria included: (1) severe comorbidities (e.g., heart disease, renal or hepatic insufficiency) precluding CDK4/6i treatment; (2) psychiatric history hindering self-assessment; (3) other malignancies within the past 5 years (excluding cured papillary thyroid carcinoma, cervical carcinoma in situ, or non-melanoma skin cancer); (4) pregnancy or lactation, or a positive baseline pregnancy test; (5) inability to adapt to AI-based intervention formats (e.g., voice or video); or (6) other conditions deemed unsuitable for participation by the investigators.

Ethics and Sample Size

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (Protocol V2.0, dated August 4, 2025). The trial was prospectively registered at ClinicalTrials.gov (NCT07409298).

Sample size was estimated using G*Power (v3.1.9.7). For a three-arm parallel RCT with SAS score as the primary endpoint, a total sample size of N=159 (n=53 per

group) was required to achieve 80% power (1-β = 0.80) at a two-sided significance level of α = 0.05, assuming a medium effect size (f = 0.25). Accounting for an anticipated 15% attrition rate, a minimum recruitment target of 187 participants was set.

A total of 200 potential participants were screened; 11 were excluded (3 ineligible; 8 declined), leaving 189 for stratified randomization. During the 24-week follow-up, 28 patients (14.8%) withdrew, with no significant difference in attrition rates between groups (P > 0.05). The final analytical cohort comprised 161 participants (Group A: 53; Group B: 54; Group C: 54).

Randomization and Statistics

Stratified randomization was implemented using SPSS (v31.0.1.0). Within each stratum, a random number sequence was generated to assign participants to Groups A, B, or C in a 1:1:1 ratio. Allocation concealment was maintained until the completion of baseline assessments. Continuous variables (e.g., age) are presented as mean ± standard deviation (SD) and compared using one-way ANOVA. Categorical variables (e.g., socioeconomic status, education) are expressed as frequencies and percentages and analyzed via Pearson's chi-squared test. All tests were two-tailed, with P < 0.05 considered statistically significant.

Interventions

All participants across the three groups received standard pharmacological guidance and health education at their respective clinical centers. In addition, differentiated management interventions were implemented as follows:

Group A (AI-driven Management Model):

Beyond routine clinical care, participants were instructed to register and utilize a WeChat mini-program named " Zhiliao Doctor " for 24 weeks of intelligent self-management. This platform was autonomously developed by the Beijing Academy of Artificial Intelligence (BAAI). In collaboration with our research team, it was tailored

for the intelligent psycho-behavioral management of patients undergoing home-based CDK4/6i therapy. The platform provided multidimensional, 24/7 personalized support, including AI emotional companionship, psychological counseling, intelligent medication and adverse event (AE) management, automated report interpretation, and proactive follow-up scheduling. The visual interface of "Smart Care MD" is presented in **Figure 1**. The core therapeutic efficacy of the platform is derived from a domain-specific medical Large Language Model (LLM) system, constructed upon a four-tier architectural framework:

(1) Foundation Model and Pre-training Tier: Utilizing a general-purpose LLM as the backbone, the system established fundamental language comprehension and logical reasoning capabilities through pre-training on massive general corpora.

(2) Medical and Psycho-emotional Fine-tuning Tier: To ensure oncological expertise and humanistic care, incremental pre-training was performed using large-scale medical texts, psychological counseling corpora, and doctor-patient dialogue datasets. Instruction Fine-tuning was employed to endow the model with emotional recognition and empathetic expression.

(3) Domain-specific Task Adaptation Tier: Three functional modules were developed to address the specificities of breast cancer treatment: ① Medical Mid-platform Module: Dedicated to specialty tasks such as clinical information extraction (e.g., lab report recognition) and specialist medical advice; ② Medical Multimodal Module: Supported image denoising and multimodal Question-Answering (QA) for automated diagnostic report interpretation; ③ Medical Emotional Dialogue Module: Leveraged Reinforcement Learning from Human Feedback (RLHF) to align interactions with human preferences and ensure that psychological counseling conformed to Cognitive Behavioral Therapy (CBT) principles.

(4) Structured Knowledge Base Support System: A dynamic repository comprising clinical guidelines, medical textbooks, expert consensuses, and knowledge graphs was integrated. Using prompt templates, the system matched real-time patient queries with

the authoritative knowledge base to provide evidence-based medication guidance and AE assessments.

Group B (Customized Proactive Follow-up Model):

This group received active, regular, and individualized management by a professional follow-up team, guided by a Standard Operating Procedure (SOP). Core interventions included:

(1) Individualized Follow-up Archives: Detailed health records, including treatment regimens and baseline psychological status, were established for each patient;

(2) Structured Proactive Tele-follow-up: Follow-up personnel conducted scheduled calls (e.g., at weeks 4 and 8) to systematically evaluate adherence, AEs, and mental health;

(3) Multichannel Routine Communication: Between calls, medication and re-examination reminders were sent via WeChat or SMS. This "human-to-human" approach emphasized trust and emotional connection.

Group C (Control Group):

Participants received standard clinical care. Healthcare providers offered routine education on medication and common AEs during outpatient visits. No systematic proactive follow-up was arranged post-visit. Patients addressed queries or discomfort through passive channels, such as self-initiated clinic visits or telephone inquiries (The measurement schedule is detailed in **Table 1**).

Figure 1 Visual Display of the "Zhiliao Doctor" Mini-program



Table 1 Schedule of Measurement Evaluations

Evaluation	**Time Point**			
	Week 0	Week 8	Week 16	Week 24
Baseline Characteristics [a]	●			
Psychological Status (SAS, SDS)	●	●	●	●
Quality of Life (EORTC QLQ-C30)	●	●	●	●
Patient-Reported Adverse Events (PRO-CTCAE)	●	●	●	●
Caregiver Psychological Status (SAS, SDS)	●			
Serological Biomarkers [b]	●	●	●	●

[a] Baseline characteristics include age, years of education, employment status, marital status, chronic diseases, and disease stage.

[b]Serological biomarkers include blood biochemistry, as well as liver and kidney function tests.

Abbreviations: SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

Outcome Measures

Primary Outcomes: Anxiety and Depression

Psychological distress was assessed using the Self-Rating Anxiety Scale (SAS)[10] and the Self-Rating Depression Scale (SDS) [11]. Both scales comprise 20 items, with each item scored on a 4-point Likert scale (1 to 4). The cumulative raw score is converted into a standardized score using a specific formula. A standardized score of 50 serves as the clinical cutoff; higher scores reflect increased severity of anxiety or depressive symptoms.

Secondary Outcomes: Quality of Life (QoL)

Quality of Life (QoL) was evaluated using the EORTC QLQ-C30 (version 3.0). This instrument includes five functional scales (physical, role, cognitive, emotional, and social), a global health status/QoL scale, three symptom scales (fatigue, nausea/vomiting, and pain), and six single items assessing common symptoms (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and perceived financial impact[12–14]. All scores were linearly transformed to a scale of 0–100 according to the EORTC scoring manual. For functional and global QoL scales, higher scores represent superior functioning and QoL. Conversely, for symptom scales and single items, higher scores indicate a greater symptomatic burden or financial distress.

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The PRO-CTCAE is a validated item library designed to characterize symptomatic adverse events (AEs). For each AE, participants evaluated up to three attributes (frequency, severity, and interference with usual activities) over the preceding seven days[15]. Attributes were scored individually or aggregated into a composite score (range: 0–3) using established mapping algorithms[16]. Based on the known safety profile of CDK4/6i and clinical relevance, 10 PRO-CTCAE symptoms were selected for this study: decreased appetite, nausea, constipation, diarrhea, dizziness, pain,

insomnia, fatigue, discouragement, and sadness[17].

Serological Biomarkers

Metabolic Profile:

Given that chronic anxiety and depression may induce dysregulation of glucose and lipid metabolism—manifesting as elevated blood glucose (GLU), triglycerides (TG), and abnormal total cholesterol (TC)—we monitored these indicators to evaluate the impact of psychological improvement on metabolic health [18].

Hepatic and Renal Function:

Chronic stress and depression can modulate liver and kidney functions via the Hypothalamic-Pituitary-Adrenal (HPA) axis, potentially leading to elevations in liver enzymes (ALT, AST) or alterations in renal parameters (Scr, BUN). These metrics were monitored to explore the potential protective effects of psychological interventions on physiological function [19,20].

Statistical Analysis

Statistical analyses were performed using SPSS (version 31.0.1.0; IBM Corp., Armonk, NY, USA), and data visualizations were generated using OriginPro 2025 (OriginLab Corp., Northampton, MA, USA) and R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables following a normal distribution are expressed as mean ± standard deviation (SD) and were compared using one-way analysis of variance (ANOVA). Categorical variables are presented as frequencies (percentages) and were analyzed via Pearson's chi-square test. To evaluate the longitudinal impact of the interventions on psychological status and quality of life (QoL), a mixed-design ANOVA was employed. This model included time (within-subject factor), group (between-subject factor), and their interaction effect. For variables exhibiting significant main or interaction effects, post-hoc multiple comparisons were conducted using the Bonferroni correction. Pearson's correlation analysis was utilized to explore the associations between psychological scores (SAS and SDS) and serological biomarkers (e.g., ALT, GLU, and GGT). Multiple Correspondence Analysis (MCA) was performed to elucidate the clustering relationships and latent associations between caregiver coping mechanisms and

sociodemographic characteristics across different intervention paradigms. All statistical tests were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

Results

Participant Flow and Baseline Comparability

A total of 200 potential participants were screened for eligibility. Following the exclusion of 11 individuals (3 who did not meet the inclusion criteria and 8 who declined to participate), 189 patients were enrolled and randomized in a 1:1:1 ratio. Participants were allocated to the AI-driven management group (Group A, n=63), the customized proactive follow-up group (Group B, n=63), and the routine follow-up group (Group C, n=63). By the 24-week study endpoint, 28 participants had withdrawn from the study (overall attrition rate: 14.8%). Importantly, no statistically significant differences in attrition rates were observed between the three study arms ($P > 0.05$). The final analytical cohort comprised 161 participants: 53 in Group A, 54 in Group B, and 54 in Group C. The detailed screening and recruitment process is illustrated in the CONSORT flow diagram (**Figure 2**).

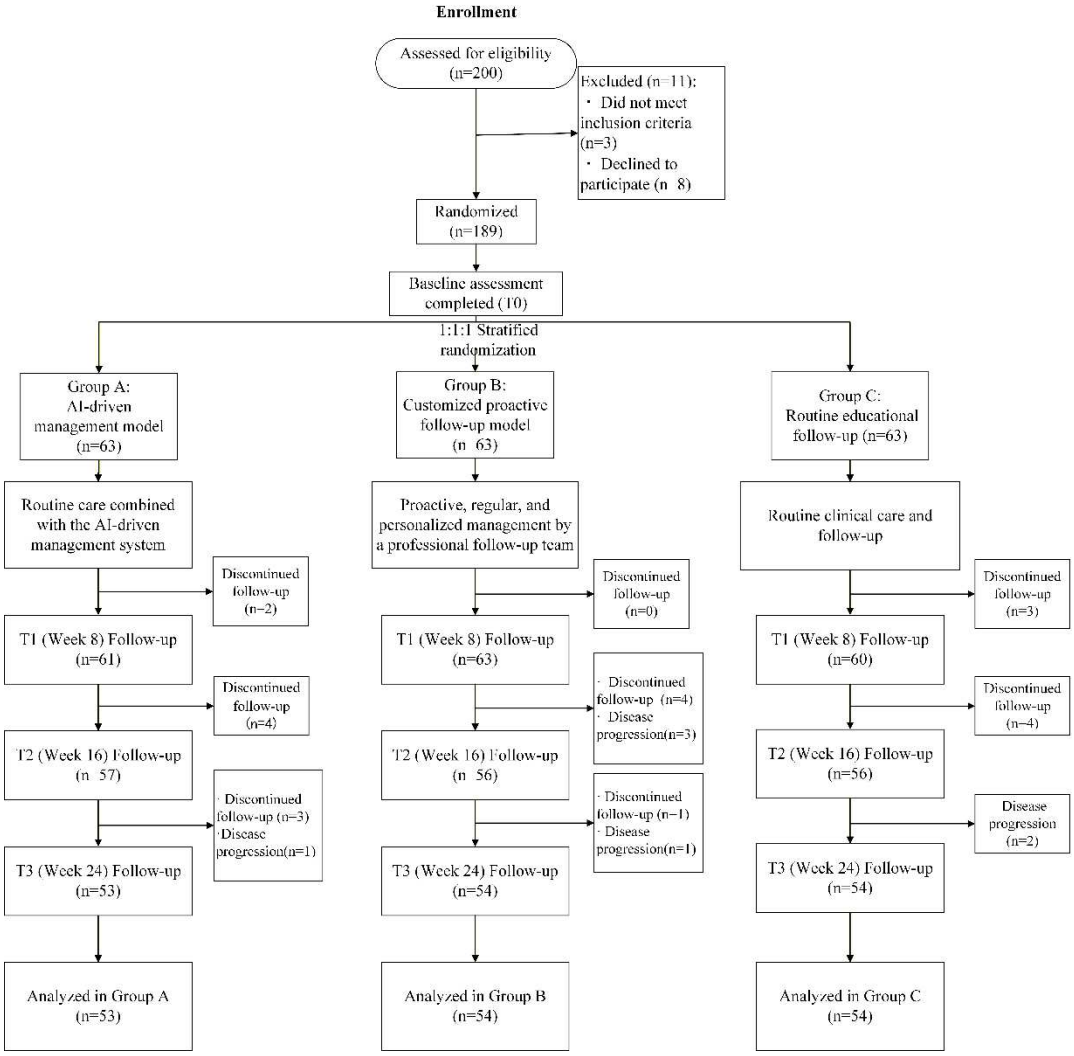


Figure 2 Study flow diagram (CONSORT Flow Diagram).

Note: Group A, AI-driven management; Group B, customized proactive follow-up; Group C, routine care. The overall attrition rate during the 24-week follow-up period was 14.8%, with no statistically significant differences in attrition rates observed between the three study arms ($P > 0.05$).

As illustrated in **Table 2**, no statistically significant differences were observed among the three groups across any of the evaluated baseline characteristics. These included age ($P = 0.334$), marital status ($P = 0.295$), as well as medical insurance type, highest educational attainment, monthly household income, and employment status (all $P > 0.05$).

Table 2 Baseline sociodemographic and clinical characteristics of the participants (N=161)

Characteristic	**Group A (n=53)**	**Group B (n=54)**	**Group C (n=54)**	**Statistic (F / χ^2)**	***P*-value**

Age (years)					
Mean±SD	52.21±10.22	49.89±9.74	52.80±12.09	1.105	0.334
Disease Stage				2.842	0.241
Early stage	28 (51.85%)	25 (47.17%)	34 (62.96%)		
Advanced stage	26 (48.15%)	28 (52.83%)	20 (37.04%)		
CDK4/6i				7.674	0.263
Ribociclib	19(35.19%)	18(33.96%)	20(37.04%)		
Dalpiciclib	13(24.07%)	16(30.19%)	18(33.33%)		
Abemaciclib	18(33.33%)	12(22.64%)	7(12.96%)		
Palbociclib	4(7.41%)	7(13.21%)	9(16.67%)		
Medical Insurance Type, n (%)				6.929	0.140
Urban Employee Insurance	26(49.1%)	38(70.4%)	30(55.6%)		
Urban/Rural Resident Insurance	26(49.1%)	16(29.6%)	24(44.4%)		
Commercial Insurance	1 (1.9%)	0 (0.0%)	0 (0.0%)		
Marital Status, n (%)				7.286	0.295
Married	47 (88.7%)	47 (87.0%)	42 (77.8%)		
Divorced	2 (3.8%)	5 (9.3%)	5 (9.3%)		
Single	3 (5.7%)	2 (3.7%)	3 (5.6%)		
Widowed	1 (1.9%)	0 (0.0%)	4 (7.4%)		
Highest Educational Level, n (%)				14.785	0.140
Primary school or below	5 (9.4%)	3 (5.6%)	7 (13.0%)		
Junior high school	10 (18.9%)	12 (22.2%)	17 (31.5%)		
High school / Technical school	18 (34.0%)	15 (27.8%)	13 (24.1%)		
Junior college	4 (7.5%)	8 (14.8%)	5 (9.3%)		
Bachelor’s degree	12 (22.6%)	16 (29.6%)	12 (22.2%)		
Postgraduate or above	4 (7.5%)	0 (0.0%)	0 (0.0%)		
Chronic				1.712	0.425

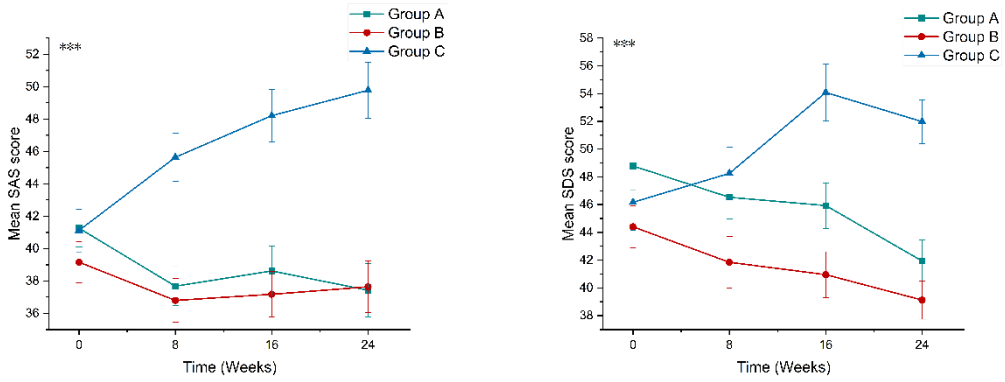
Diseases, n (%)					
Yes	14 (26.4%)	12 (22.2%)	18 (33.3%)		
No	39 (73.6%)	42 (77.8%)	36 (66.7%)		
Monthly Household Income (CNY), n (%)				6.284	0.179
< 3000	20 (37.7%)	16 (29.6%)	25 (46.3%)		
3000-7999	19 (35.8%)	18 (33.3%)	20 (37.0%)		
≥8000	14 (26.4%)	20 (37.0%)	9 (16.7%)		
Presence of Children, n (%)				3.967	0.138
Yes	52 (98.1%)	51 (94.4%)	48 (88.9%)		
No	1 (1.9%)	3 (5.6%)	6 (11.1%)		
Accompanied by Family, n (%)				1.308	0.520
Yes	46 (86.8%)	45 (83.3%)	49 (90.7%)		
No	7 (13.2%)	9 (16.7%)	5 (9.3%)		
Employment Status, n (%)				7.861	0.642
Agricultural worker	10 (18.9%)	7 (13.0%)	6 (11.1%)		
Full-time	9 (17.0%)	17 (31.5%)	14 (25.9%)		
Part-time	0 (0.0%)	1 (1.9%)	2 (3.7%)		
Homemaker	5 (9.4%)	8 (14.8%)	8 (14.8%)		
Unemployed	6 (11.3%)	5 (9.3%)	5 (9.3%)		
Retired	23 (43.4%)	16 (29.6%)	19 (35.2%)		

Primary Outcomes

At baseline, the prevalence of anxiety (SAS score ≥ 50) was 19.3% (31/161), categorized as mild (16.8%, n=27), moderate (1.9%, n=3), and severe (0.6%, n=1). The prevalence of depression (SDS score ≥ 50) was 41.0% (66/161), including mild (23.6%, n=38), moderate (13.7%, n=22), and severe cases (3.7%, n=6).

Mixed-design ANOVA revealed significant group × time interaction effects for both anxiety and depression (see **Figure 3**).

Specifically, the interaction effects were highly significant for SAS scores (F = 5.961, $P < 0.001$) and SDS scores (F = 4.931, $P < 0.001$), suggesting that the longitudinal trajectories of psychological distress diverged significantly across the three groups. Further simple effect analysis elucidated a clear divergence in psychological trajectories during follow-up: Psychological status in the control group (Group C) deteriorated significantly alongside treatment progression, with SDS scores exhibiting an upward trend that peaked at Week 16 (T2). In contrast, the intervention groups (Groups A and B) demonstrated superior regulatory efficacy; SAS levels remained stable throughout the study, while SDS scores exhibited a progressive and steady decline (all $P < 0.001$). Overall, the efficacy of Groups A and B in maintaining psychological stability and ameliorating depressive symptoms was significantly superior to that of Group C at all post-baseline follow-up time points.



Anxiety (SAS) Comparison Curves Depression (SDS) Comparison Curves

Figure 3 Longitudinal trajectories of SAS and SDS scores across the three study groups during the 24-week follow-up.

Note: Data are presented as mean ± SEM. Mixed-design ANOVA was used to assess the interaction between time and intervention. Statistical significance relative to Group C: *$P <$ 0.05, **$P < 0.01$, ***$P < 0.001$. T0, baseline; T1, Week 8; T2, Week 16; T3, Week 24.

To further elucidate the specific inter-group differences, post-hoc multiple comparisons using the Bonferroni correction were performed for each follow-up timepoint, with the results summarized in **Tables 3** and **Table 4**.

Table 3 Multiple Comparisons of Self-Rating Anxiety Scale (SAS) Scores Among Three Groups

(Bonferroni Method)

Time Point	Comparison Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
T0	Group A vs Group B	2.229	1.949	0.764	(-2.49, 6.95)
	Group A vs Group C	0.320	1.917	1.000	(-4.33, 4.97)
	Group B vs Group C	-1.910	1.939	0.979	(-6.61, 2.79)
T1	Group A vs Group B	0.861	1.803	1.000	(-3.51, 5.23)
	Group A vs Group C	-7.945*	1.774	<0.001	(-12.24, -3.65)
	Group B vs Group C	-8.806*	1.794	<0.001	(-13.15, -4.46)
T2	Group A vs Group B	1.398	2.236	1.000	(-4.02, 6.82)
	Group A vs Group C	-9.593*	2.200	<0.001	(-14.93, -4.26)
	Group B vs Group C	-10.990*	2.225	<0.001	(-16.38, -5.60)

Time Point	Comparison Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
T3	Group A vs Group B	-0.240	1.832	1.000	(-4.68, 4.20)
	Group A vs Group C	-12.346*	1.803	<0.001	(-16.72, -7.98)
	Group B vs Group C	-12.106*	1.823	<0.001	(-16.52, -7.69)

Note: Group A: AI-based Management Model; Group B: Customized Active Follow-up Model; Group C: Routine Follow-up Model. *denote statistical significance at $P < 0.05$ (Bonferroni-adjusted).

Table 4 Multiple Comparisons of Self-Rating Depression Scale (SDS) Scores Among Three Groups (Bonferroni Method)

Time Point	Comparison Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
T0	Group A vs Group B	4.383	2.530	0.256	(-1.75, 10.52)
	Group A vs Group C	2.617	2.530	0.909	(-3.52, 8.75)
	B 组 vs C 组	-1.766	2.530	1.000	(-7.90, 4.37)
T1	Group A vs	4.681	2.526	0.198	(-1.44, 10.80)

Time Point	Comparison Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
	Group B				
	Group A vs Group C	-1.723	2.526	1.000	(-7.84, 4.40)
	Group B vs Group C	-6.404*	2.526	0.037	(-12.53, -0.28)
T2	Group A vs Group B	4.979	2.529	0.153	(-1.15, 11.11)
	Group A vs Group C	-8.149*	2.529	0.005	(-14.28, -2.02)
	Group B vs Group C	-13.128*	2.529	<0.001	(-19.26, -7.00)
T3	Group A vs Group B	2.809	2.116	0.560	(-2.32, 7.94)
	Group A vs Group C	-10.043*	2.116	<0.001	(-15.17, -4.91)
	Group B vs Group C	-12.851*	2.116	<0.001	(-17.98, -7.72)

Note: Group A: AI-based Management Model; Group B: Customized Active Follow-up Model; Group C: Routine Follow-up Model. *denote statistical significance at $P < 0.05$ (Bonferroni-adjusted).

As shown in **Table 3**, during the early stage of intervention (week 8, T1), the

anxiety levels in both the artificial intelligence group (Group A) and the customized active follow-up group (Group B) were already significantly lower than those in the standard care group (Group C) (both $P < 0.001$), and this psychological stability advantage was sustained until the follow-up endpoint (week 24, T3). No statistically significant differences in anxiety control efficacy were observed between Groups A and B at any follow-up timepoint (all $P = 1.000$).

Regarding depression control (**Table 4**), the standard care group (Group C) deteriorated significantly as the treatment cycle progressed, with depression scores peaking at week 16 (T2). Customized active follow-up (Group B) demonstrated a faster onset window, significantly reducing depression scores as early as week 8 (T1) compared with Group C ($P = 0.037$). In contrast, the intelligent AI management (Group A) exhibited a certain delayed benefit effect, with the difference reaching statistical significance at week 16 (T2) ($P = 0.005$). By the follow-up endpoint at week 24 (T3), Groups A and B showed comparable efficacy in alleviating depression, and both were significantly superior to Group C (both $P < 0.001$).

Secondary Outcomes

Quality of Life (QoL) ：

The QoL of participants across the three arms was longitudinally evaluated using the EORTC QLQ-C30, encompassing global health status and five primary functional domains. The results revealed that the impacts of different intervention paradigms were characterized by significant domain-specificity, as detailed in **Table 5**、**Table 6** and **Figure 4**.

For cognitive, emotional, and social functioning, as well as global health status, mixed-design ANOVA demonstrated significant group × time interaction effects (all $P < 0.05$). Inter-group comparisons indicated that both intervention cohorts (Groups A and B) achieved significantly superior scores compared to the control group (Group C) at the study endpoint (T3; all $P < 0.05$). Although numerical variances were observed between Groups A and B in these dimensions, the differences did not reach

statistical significance (all $P > 0.05$). No statistically significant differences were observed among the three groups regarding physical functioning and role functioning (all $P > 0.05$).

Table 5 Longitudinal changes in EORTC QLQ-C30 domain scores across the three groups (Mean ± SD)

Domain	Group	T0 (Baseline)	T1 (Week 8)	T2 (Week 16)	T3 (Week 24)
Global Health	Group A	62.5 ± 12.1	68.4 ± 11.5	74.5 ± 10.2	78.2 ± 9.5
	Group B	61.8 ± 11.8	71.2 ± 11.0	75.8 ± 10.5	79.5 ± 9.8
	Group C	62.1 ± 12.3	58.5 ± 12.8	54.2 ± 13.5	51.0 ± 14.2
Cognitive Functioning	Group A	72.5 ± 9.5	76.8 ± 9.2	80.5 ± 8.8	84.2 ± 8.5
	Group B	71.8 ± 9.8	74.5 ± 9.0	78.0 ± 8.5	81.5 ± 8.2
	Group C	72.2 ± 10.0	68.5 ± 10.5	64.2 ± 11.0	60.5 ± 11.5
Emotional Functioning	Group A	55.4 ± 11.5	65.2 ± 10.8	75.5 ± 9.5	80.5 ± 8.5
	Group B	56.2 ± 11.2	68.5 ± 10.5	78.2 ± 9.2	83.5 ± 8.2
	Group C	55.8 ± 11.8	52.4 ± 12.0	48.5 ± 12.5	45.2 ± 13.0
Social Functioning	Group A	60.5 ± 14.2	66.8 ± 13.5	72.5 ± 12.0	76.8 ± 11.5
	Group B	59.8 ± 14.5	68.5 ± 13.0	75.2 ± 11.8	79.5 ± 11.0
	Group C	60.2 ± 14.8	55.4 ± 15.2	49.5 ± 15.8	44.2 ± 16.5
Physical Functioning	Group A	75.2 ± 10.5	73.5 ± 10.2	71.0 ± 9.8	70.5 ± 9.2
	Group B	74.8 ± 10.8	74.0 ± 10.0	71.5 ± 9.5	70.2 ± 9.0
	Group C	75.0 ± 11.0	72.5 ± 11.5	70.2 ± 12.0	69.8 ± 12.5
Role Functioning	Group A	68.5 ± 13.2	66.0 ± 12.5	64.5 ± 11.8	63.2 ± 11.0
	Group B	69.1 ± 12.8	67.5 ± 12.0	65.2 ± 11.5	64.5 ± 10.8
	Group C	68.8 ± 13.5	65.5 ± 14.0	63.8 ± 14.5	62.5 ± 15.0

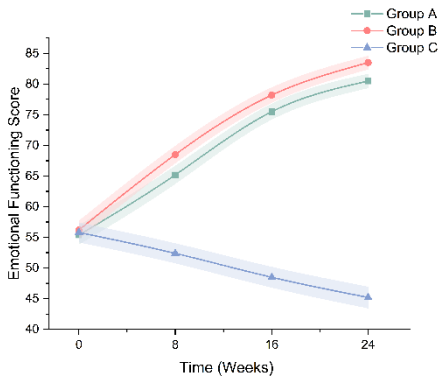
Note: Group A, AI-driven management; Group B, customized proactive follow-up; Group C, routine care. QoL scores range from 0 to 100, with higher scores in functional domains and global health indicating superior functioning and better quality of life. SD, standard deviation.

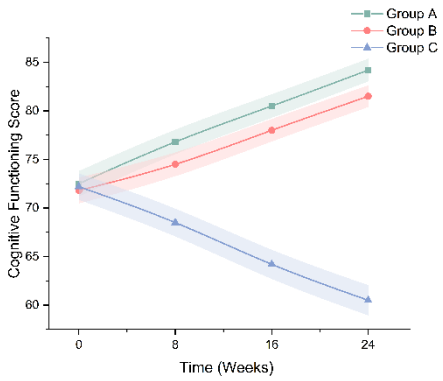
Table 6 Comparison of Functional Domain Scores and Global Health Status Among the Three Groups (EORTC QLQ-C30)

Assessment Indicators (Domain)	P_{T0} (Baseline)	P_{T3} (Inter-group)	Group A vs. Group B	Group A vs. Group C	Group B vs. Group C

Global Health Status / QoL	0.956	< 0.001	0.488	< 0.001	< 0.001
Cognitive Functioning	0.933	< 0.001	0.097	< 0.001	< 0.001
Emotional Functioning	0.937	< 0.001	0.066	< 0.001	< 0.001
Social Functioning	0.969	< 0.001	0.217	< 0.001	< 0.001
Physical Functioning	0.982	0.940	0.865	0.743	0.849
Role Functioning	0.973	0.698	0.539	0.784	0.428

Note: Group A: AI-based Management Model; Group B: Customized Active Follow-up Model; Group C: Routine Follow-up Model. P_{T0} represents the significance level for baseline balance testing; P_{T3} represents the significance level for inter-group comparisons at Week 24. Significant P-values ($P < 0.05$) are highlighted in bold.





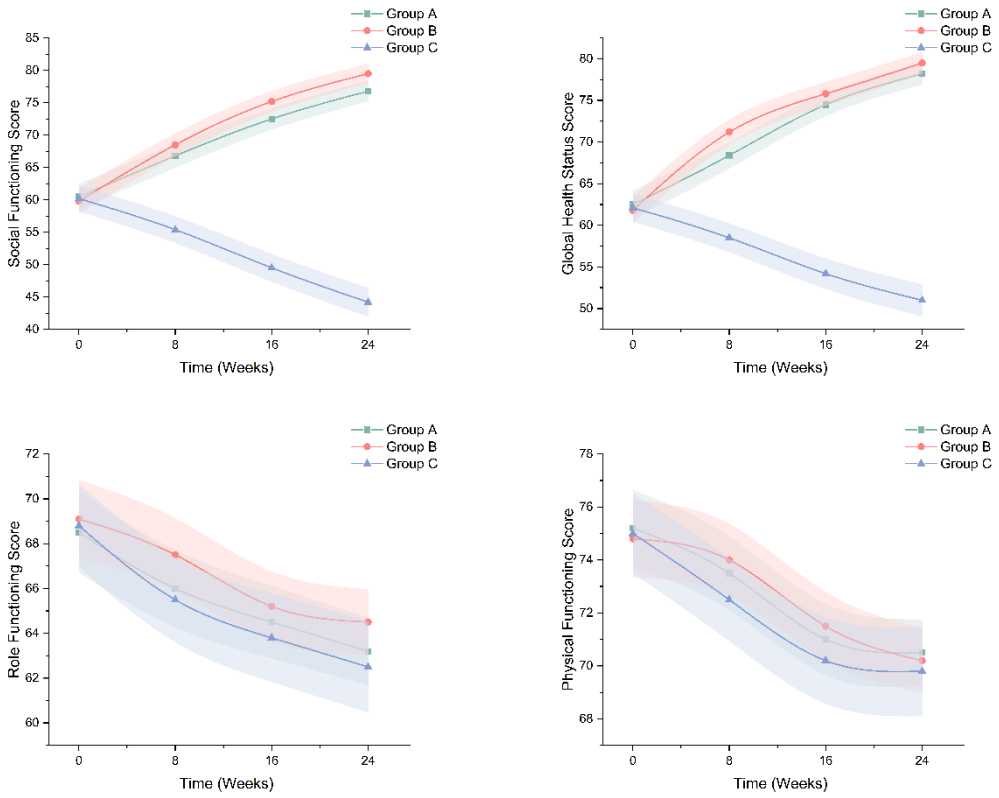


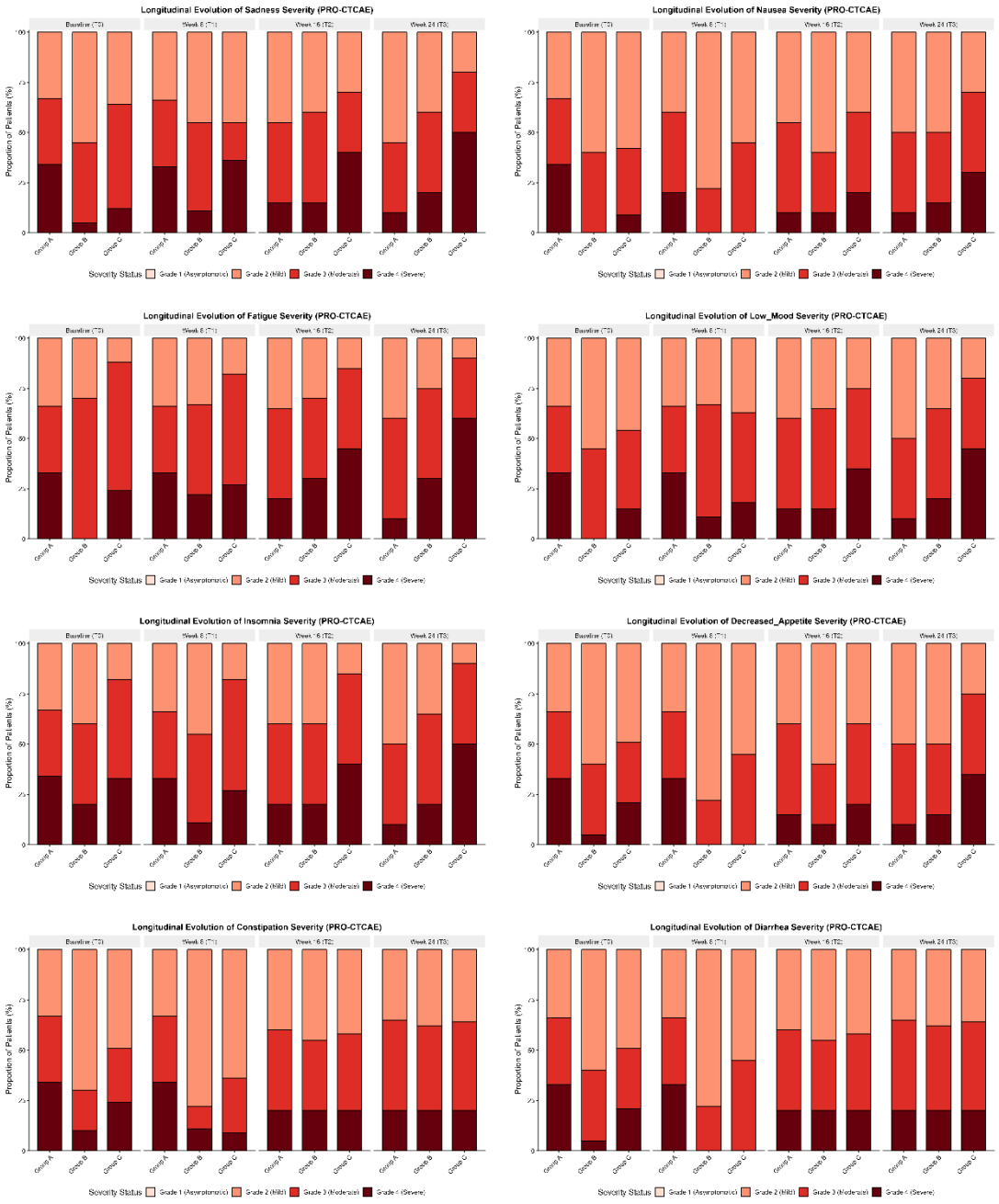
Figure 4 Longitudinal trajectories of quality of life (QoL) functional domains across the three study groups.

*Note:*The figure depicts the dynamic evolution of six domains from the EORTC QLQ-C30: cognitive functioning, emotional functioning, social functioning, physical functioning, role functioning, and global health status. Shaded error bands represent the mean ± SEM.

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The longitudinal trajectory of symptomatic adverse events (AEs) was monitored from baseline to Week 24. Our analysis revealed that the efficacy of the different management models was highly symptom-specific. For subjective symptomatic toxicities, including fatigue, insomnia, mood fluctuations, nausea, and decreased appetite, the routine care group (Group C) exhibited a significant escalation in the prevalence of moderate-to-severe symptoms (equivalent to CTCAE Grade 3–4) as treatment cycles progressed. In contrast, the AI-driven group (Group A) successfully maintained the majority of patients within the asymptomatic-to-mild range (Grade 0–2). This mitigation of symptom exacerbation was attributed to the AI platform's capacity for early signal detection and prompt, closed-loop intervention for low-grade

symptoms, which effectively prevented their progression to higher-grade severities. Conversely, for pharmacologically-driven toxicities—specifically constipation, diarrhea, and dizziness—the severity trajectories remained consistent across all three study arms. No statistically significant inter-group differences were observed ($P > 0.05$), suggesting these AEs are primarily inherent to the pharmacodynamic profile of CDK4/6i therapy (**Figure 5**).



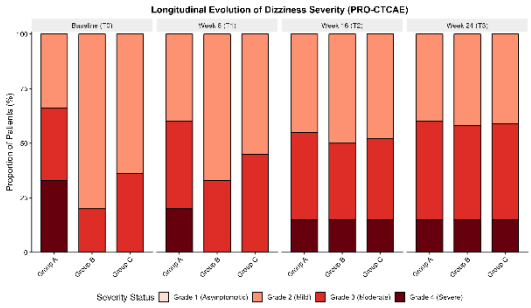


Figure 5 Longitudinal evolution of symptomatic adverse event severity (PRO-CTCAE) among the three study groups.

Note: Based on the PRO-CTCAE measurement system, symptom severity is graded as Grade 1 (asymptomatic), Grade 2 (mild), Grade 3 (moderate), and Grade 4 (severe). The stacked bars illustrate the proportion of patients within each severity category across the four follow-up time points.

Correlation and Comparative Analysis of Serological Biomarkers and Psychological Status

Correlation Assessment: A broad assessment of the associations between serological continuous variables and psychological scores (SAS and SDS) was conducted using Pearson's correlation analysis (**Figure 6**). Preliminary results identified significant positive correlations between alanine aminotransferase (ALT) and both SAS scores ($r = 0.178$, $P < 0.05$) and SDS scores ($r = 0.254$, $P < 0.01$). Additionally, fasting glucose (GLU) was significantly correlated with SAS ($r = 0.221$, $P < 0.05$), while gamma-glutamyl transferase (GGT) showed a significant correlation with SDS ($r = 0.229$, $P < 0.01$).

Categorical Validation: Following the initial heatmap screening, indicators were dichotomized into "normal" and "abnormal" groups based on the upper limit of normal (ULN) for further validation. This refined analysis revealed that only the abnormal elevation of ALT maintained robust statistical significance in association with intensified anxiety and depression. Specifically, using a clinical threshold of ALT = 40 U/L (1 × ULN), the elevated ALT group exhibited significantly higher SAS scores compared to the normal group ($P < 0.01$), with an even more pronounced increase in SDS scores ($P < 0.001$). An advanced stratified analysis was performed for depressive symptoms (SDS) using a higher threshold of ALT $\geq 1.5 \times$ ULN

(**Figure 7**). The results indicated that even after excluding the interference of mild transaminase fluctuations, the SDS scores of patients in the ALT $\geq$ 1.5 $\times$ ULN group remained significantly higher than those in the control group (P < 0.01).

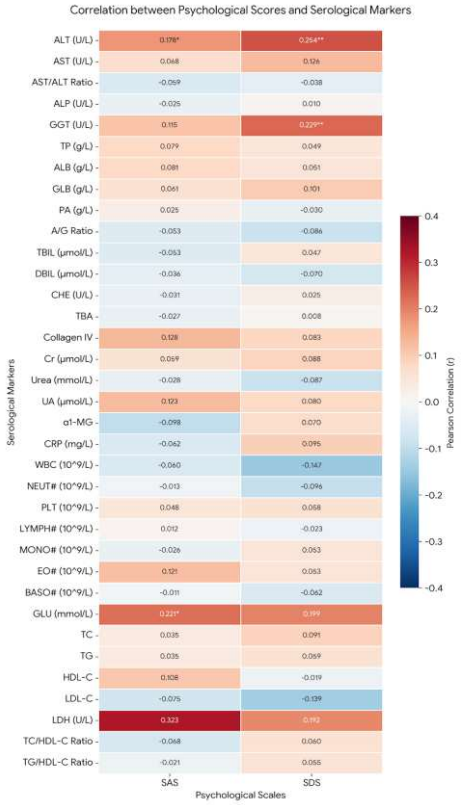


Figure 6 Pearson correlation heatmap between serological continuous variables and psychological status scores.

Note: The color and intensity of each cell represent the direction and magnitude of the Pearson correlation coefficient (r). Red indicates a positive correlation, and blue indicates a negative correlation.

ALT, alanine aminotransferase; **GLU**, fasting glucose; **GGT**, gamma-glutamyl transferase; **SAS**, Self-Rating Anxiety Scale; **SDS**, Self-Rating Depression Scale. Statistical significance is indicated by $P < 0.05$ *and* $^{**}P < 0.01$.

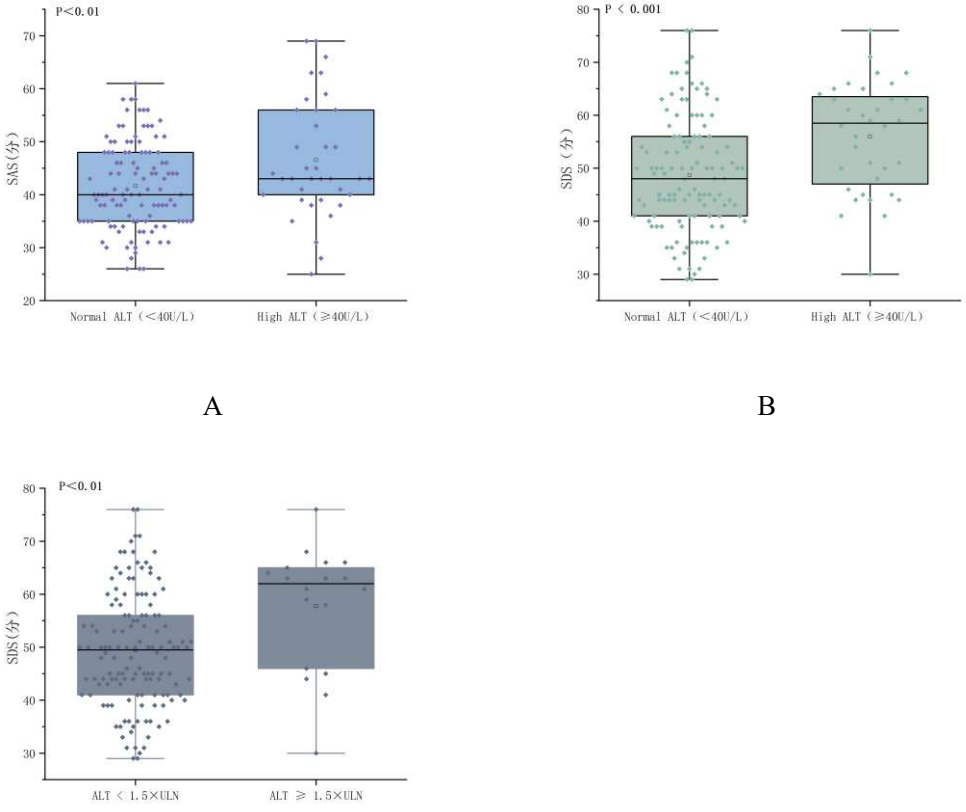


Figure 7 Comparative analysis of anxiety and depression scores based on distinct clinical ALT thresholds.

Note: Panels A and B present group comparisons using the upper limit of normal (ALT = 40 U/L) as the cut-off. Panel C illustrates the comparison of depression scores based on the clinical intervention threshold for liver injury (ALT $\geq$ 1.5 $\times$ ULN, i.e., 60 U/L). Data are expressed as Mean $\pm$ SD. Inter-group comparisons were conducted using the independent samples t-test. ULN, upper limit of normal.

Multiple Correspondence Analysis of Patient-Caregiver Psychological Status and Socioeconomic Characteristics

MCA Model Overview: A Multiple Correspondence Analysis (MCA) incorporating 13 categorical variables was conducted. The first two dimensions accounted for 31.7% of the total inertia (Dim 1: 17.2%; Dim 2: 14.5%), effectively elucidating the primary association patterns between familial psychological status and sociodemographic characteristics (**Figure 8**).

Dimension 1 primarily reflected socioeconomic background: the positive pole

clustered socioeconomic advantage categories, such as high income, tertiary education or above, and urban employee medical insurance, whereas the negative pole represented vulnerable categories.

Emotional Covariation Patterns: The MCA results demonstrated a robust positive association between patient and caregiver psychological states. Within the 2D MCA coordinate plane, the categories "Patient: Depression (+)", "Caregiver: Depression (+)", and "Caregiver: Anxiety (+)" clustered closely in the positive region of Dimension 1. These points exhibited high contribution rates (contrib), as indicated by the warmer color mapping. Conversely, asymptomatic categories (the "Negative" status) were concentrated in the negative region of Dim 1, forming a sharp contrast with the symptomatic clusters. This spatial distribution underscores a high degree of emotional concordance between patients and their caregivers.

Furthermore, this emotional clustering pattern aligned with clinical features such as "fixed caregiving" and "comorbid chronic diseases" within the same quadrant, suggesting these factors may act as critical mediators exacerbating dyadic emotional distress.

Conclusion: These findings suggest that clinical interventions should move beyond the individual and adopt "family-centered" integrated psychological support strategies to optimize overall therapeutic outcomes.

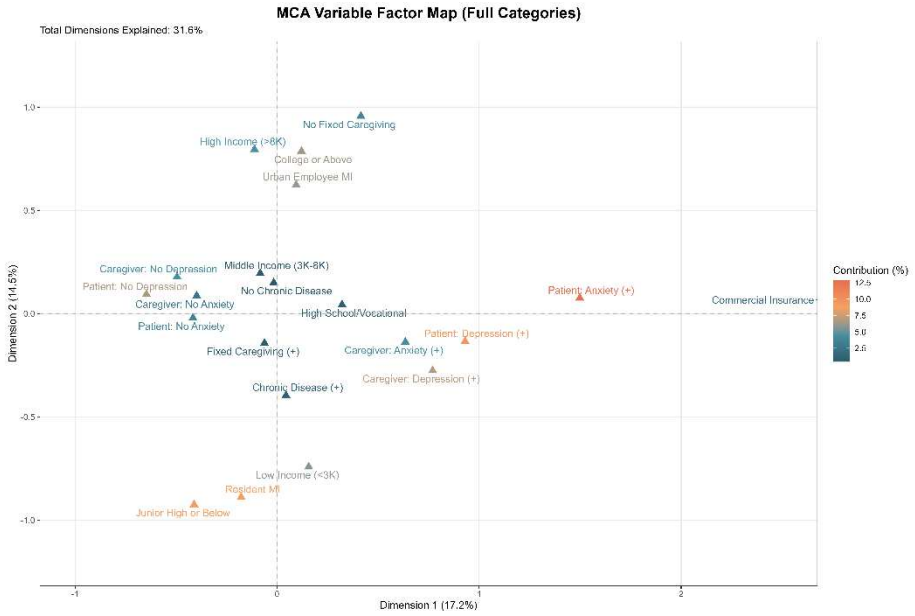


Figure 8 Variable factor map of Multiple Correspondence Analysis (MCA) for patient-caregiver characteristics.

Note: This figure presents the dimensionality-reduced projection of 13 analytical categories across a two-dimensional space. Dimension 1 (17.2%) is predominantly defined by socioeconomic background variables, while Dimension 2 (14.5%) primarily reflects the psychological burden of caregivers. The spatial proximity between categories in the plot indicates the degree of their statistical association; closer proximity signifies a stronger correlation between the corresponding categorical traits.

Discussion

This study, through a multi-center randomized controlled trial (RCT), systematically evaluated the multidimensional impacts of an AI-driven management model, a customized follow-up model, and routine care on patients receiving home-based CDK4/6 inhibitor (CDK4/6i) therapy.

The research findings confirmed that active interventions—whether via an AI-driven intelligent platform or professional human follow-up—were significantly superior to the traditional routine management model in both stabilizing patients' anxiety and alleviating their depressive states.

1.Differential Efficacy of AI and Customized Follow-up in Psychological Stability

CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy are the standard-of-care for

HR+/HER2− advanced breast cancer. The oral regimen shifts care to out-of-hospital settings, where prolonged toxicity accumulation and social isolation often exacerbate psychological distress [21,22]. Our findings demonstrate that both AI-driven management (Group A) and customized proactive follow-up (Group B) significantly attenuated anxiety and depression compared with routine care (Group C) ($P < 0.001$). While Group C experienced peak depressive symptoms at Week 16 (T2), active interventions maintained longitudinal psychological stability. Post-hoc analysis revealed a distinct temporal pattern: Group B achieved rapid depression relief by Week 8 ($P = 0.037$), whereas Group A exhibited a delayed therapeutic gain becoming statistically significant at Week 16 ($P = 0.005$). This latency reflects the cognitive acclimatization period required for patients to transition from "instrumental usage" to "emotional trust" in AI platforms[23]. Nevertheless, both models yielded equivalent long-term efficacy at Week 24, confirming that continuous AI engagement counterbalances its initial latency [24,25].

2. Domain-Specific Impact of Intervention Models on Quality of Life Dimensions

Active management significantly improved cognitive, emotional, and social functioning, as well as global health status ($P < 0.05$). Notably, Group A achieved the highest cognitive function scores, likely attributable to automated medication reminders and report interpretations that reduced decisional burden. Conversely, no inter-group differences were observed in physical or role functioning ($P > 0.05$)[26,27]. This highlights that drug-induced physiological depletion (e.g., myelosuppression and fatigue) cannot be directly reversed by psychological care[28]. Clinical interventions should thus focus on enhancing patients' psychological resilience and symptom adaptation rather than promising physical restoration.

3. Advantages of the AI Management Model in Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE)

For subjective symptoms (e.g., fatigue, insomnia, mood fluctuations, and

nausea), Group A effectively contained symptom severity within Grade 1–2, significantly lowering Grade 3–4 incidence relative to Group C. This advantage stems from the AI platform's real-time symptom capture and closed-loop guidance [29,30]. In contrast, pharmacologically driven toxicities (e.g., diarrhea and constipation) showed uniform trajectories across groups, confirming that while AI cannot alter inherent drug toxicity, it enhances home-care safety through early signal detection.

4. Correlation Between Psychological Status and Serological Indicators: Evidence of Psychophysiological Link

Pearson analysis revealed significant positive correlations between anxiety/depression scores and serum ALT levels ($r = 0.178–0.254,\ P < 0.05$). Stratified analyses confirmed that patients with abnormal ALT (≥ 40 U/L) or clinically actionable liver injury ($\geq 1.5 \times$ ULN) exhibited significantly higher depression scores ($P < 0.01$). Chronic psychological stress activates the HPA axis and sympathetic system, inducing systemic inflammation and hepatic oxidative stress [20,31]. Given that CDK4/6i (e.g., abemaciclib, ribociclib) undergo hepatic CYP3A4 metabolism[32], stress-induced microenvironmental distress may compound metabolic burdens[33]. Thus, clinicians should routinely evaluate psychological stress alongside DILI screening in patients with transaminase fluctuations.

5. Association Between Patient and Caregiver Psychological Status: Insights from MCA Results

Multiple Correspondence Analysis (Dim 1: 17.2%, Dim 2: 14.5%) demonstrated strong positive spatial clustering among patient anxiety/depression, caregiver distress, fixed caregiving, and chronic comorbidities. This confirms an "intra-family emotional contagion," where caregiving strain synchronizes dyadic distress. Advantageous socioeconomic status (high income, tertiary education) clustered in opposing quadrants, indicating a protective buffering capacity against distress. These findings support shifting from individual-centric care to "family-centered" integrated psychological support[34,35].

6. Clinical Significance and Innovations

In collaboration with the BAAI, this study is the first to construct and validate a domain-specific medical LLM platform ("Zhiliao Doctor") for home-based CDK4/6i care. Built on a four-tier architecture (Foundation LLM → Medical/Psychological Fine-tuning → Task Adaptation → Knowledge Base), the system bridges LLM empathy, real-time PRO-CTCAE monitoring, and clinical guidelines. Compared to labor-intensive human follow-up, the AI paradigm offers near-zero marginal cost, 24/7 scalability, reduced clinical burden, and objective cloud-shared longitudinal data tracking.

7. Research Limitations

Although this study systematically compared various intervention models within the framework of the "bio-psycho-social" medical model, several limitations remain: First, the 24-week follow-up period is relatively short; the translational benefits of active intervention on long-term survival outcomes (e.g., PFS, OS) still require validation through long-term follow-up cohorts. Second, due to the high dependence of AI intervention on smart mobile devices, this study may be subject to selection bias regarding the elderly or populations with limited digital literacy. Third, the observed correlation between psychological scores and liver function abnormalities lacks empirical support from direct biochemical mechanisms, such as levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and neuroendocrine hormones. Future studies should consider incorporating multi-omics technologies and longer follow-up periods to further elucidate the molecular mechanisms by which psychological interventions improve physiological outcomes in oncology patients.

Conclusion

This study, through a multi-center randomized controlled trial (RCT), confirmed the significant efficacy of an AI-driven management model and customized follow-up in improving the psychological and behavioral outcomes of breast cancer patients

receiving home-based CDK4/6i therapy. Results demonstrated that active interventions effectively stabilized patient anxiety and significantly reduced depression scores. Notably, the AI model exhibited long-term efficacy equivalent to human follow-up and demonstrated superior performance in improving cognitive function through intelligent reminders. Simultaneously, AI management significantly enhanced early-warning capabilities for adverse events and the safety of home-based treatment by capturing PRO-CTCAE symptoms in real-time. Furthermore, Pearson correlation analysis revealed a significant positive correlation between patients' psychological scores and ALT levels, providing clinical empirical evidence for the "liver-brain axis" mechanism. Additionally, Multiple Correspondence Analysis (MCA) confirmed the phenomenon of familial emotional covariation and the buffering role of socioeconomic resources. In conclusion, the AI management model provides a solid evidence-based foundation for constructing a new "Bio-Psycho-Social" intelligent paradigm for oncology continuity-of-care.

Conflict of interest statement

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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