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Dynamic screening for anxiety and depression in patients undergoing primary surgery for gastrointestinal cancer

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KEY WORDS

anxiety, depression, disease-free survival, gastrointestinal cancers, immune

ABSTRACT

INTRODUCTION Anxiety and depression are persistent problems among patients with gastrointestinal (GI) cancers.

AIM This study aimed to evaluate the efficacy of time-dynamic screening for anxiety and depression in patients undergoing primary surgery for GI cancers.

MATERIALS AND METHODS A total of 876 individuals were reviewed. The patients who underwent dynamic screening for anxiety and depression were selected as the screening cohort. A 1:1 propensity--score matching was performed for the controls. The primary end point was 1-year disease-free survival (DFS). Secondary outcomes included inflammatory cytokine levels, leukocyte counts, and scores from the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 item (GAD-7), and the 5-level European Quality of Life Five-dimension (EQ-5D-5L) assessment.

RESULTS One-year DFS was higher among the screening cohort than the controls (91.4% vs 81.2%; $P < 0.001$). The levels of anxiety and depression decreased over time in the screening cohort, with lower mean (SD) PHQ-9 scores of 8.19 (1.32) 1 month postoperatively and 6.9 (1.33) at 3-month follow-up ($P < 0.001$), and lower mean (SD) GAD-7 scores of 7.73 (3.94) 1 month after surgery and 5.01 (3.31) 3 months postoperatively ($P < 0.001$), as compared with the controls. At 3 months postsurgery, the screening cohort showed better outcomes than the controls in terms of the levels of interleukin-6 ($P = 0.003$) and tumor necrosis factor α ($P < 0.001$), as well as the CD3+ cell count ($P = 0.02$), CD4+/CD8+ ratio ($P = 0.02$), and natural killer cell count ($P = 0.006$). The patients undergoing screening exhibited greater improvements in the EQ-5D-5L scores over time than the controls ($P < 0.001$). Minor adverse events were observed in 8.2% of the screening cohort.

CONCLUSIONS Time-dynamic screening for GI cancers effectively reduces anxiety and depression after surgery, improves immune function, and enhances quality of life, thus contributing to a better prognosis at 1 year follow-up.

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INTRODUCTION Gastrointestinal (GI) cancers are malignant diseases that account for one-third of all cancer-related deaths worldwide.[1] Eastern Asia had the highest lifetime risk of developing and dying from GI cancers in 2020.[2] In China, GI cancers comprised 38.8% of all cancer cases recorded in 2020, posing a heavy health burden with an age-standardized disability-adjusted life--years of 1311.4.[3] Based on a systematic review and meta-analysis, anxiety and depression have been identified as common among these patients, with a pooled prevalence of 20.4% for anxiety and 30.2% for depression.[4] More than 50% of the patients undergoing primary surgery experienced at least mild anxiety or depression during the perioperative period.[5] It not only increases the psychological stress on patients but also reduces their adherence to treatment, which negatively impacts immune function, disease prognosis, and patients' quality of life (QoL).[6] According to the European Society for Medical Oncology Clinical Practice Guideline,[7] multiple treatments,

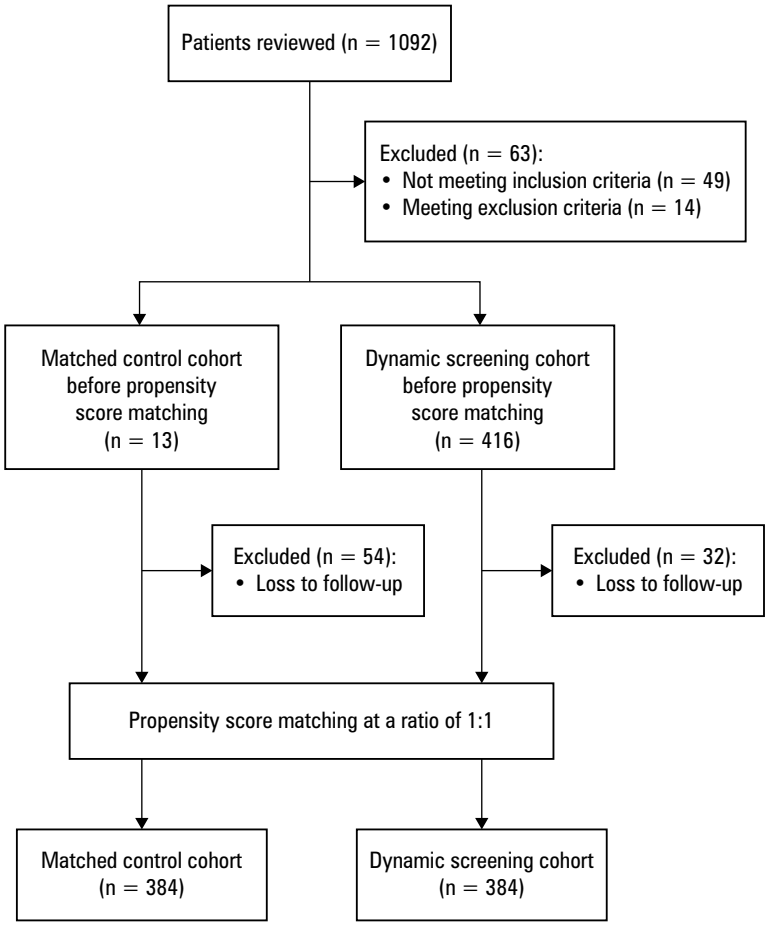

FIGURE 1 Flow diagram of the study cohorts

such as psychotherapy, cognitive behavioral therapy, mindfulness-based therapy, and psychopharmacological therapy, are effective for managing anxiety and depression in cancer patients. Although there is currently no standardized protocol, a series of recommendations for regular screening, assessment, and management of these symptoms has been developed in oncology settings.[8]

AIM Since formal routine screening was the initial step in the management protocol during the perioperative period, this study was initially conducted to evaluate the effect of time-dynamic screening followed by psychological interventions for anxiety and depression on the clinical outcomes of patients who underwent surgery for GI cancers.

MATERIALS AND METHODS This retrospective propensity score-matched (PSM) cohort study was conducted in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.[9] Between January 1, 2022 and July 31, 2024, patients undergoing primary surgery for GI cancers were identified through a review of electronic medical records (EMRs). The inclusion criteria were as follows: 1) a confirmed diagnosis of gastric or colorectal cancer according to the criteria of the Chinese Society of Clinical Oncology Clinical guidelines[10,11]; 2) age below18 years; 3) cancer stage I–III; and 4) minimum 1-year follow-up. Patients were excluded if they had other malignant tumors, a history of anxiety or depression within 2 years before the GI cancer diagnosis, severe complications from GI cancer surgery, other psychiatric disorders, cognitive impairment, alcohol addiction, severe hepatic or renal dysfunction, severe cardiovascular disease, a history of emergency surgery for GI cancers, pregnancy/lactation, or incomplete medical data.

Dynamic screening was initiated based on patient selection that most closely aligned with their preference after consultation with their doctor. The patients were screened during a 5-minute clinical interview, which was conducted within 72 hours before surgery, as well as at 1 and 3 months postoperatively during their routine visits. During the face-to-face interviews, a questionnaire survey was administered using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 item (GAD-7) scale. Referrals to a psychologist for specialized assessments were recommended for the patients with positive results, who received a total score of 5 or greater in either the PHQ-9 or GAD-7 questionnaire, enabling timely intervention or support.

The PSM method was employed to match the patients who underwent dynamic screening with those who did not at a 1:1 ratio. Propensity scores were calculated using multivariable logistic regression by the nearest matching with a caliper width of 0.2. The confound covariables were: age, sex, ethnicity, body mass index, cancer type, disease duration, tumor-node-metastasis stage, American Society of Anesthesiologists classification, type of surgery, adjunctive chemoradiotherapy, comorbidities, immune function, clinical depression level, and clinical anxiety level.

The patients' demographic and clinical data were extracted from their EMRs. Follow-up data were collected by clinicians during visit interviews. Immune function was assessed by the flow cytometry analysis of CD3+, CD4+, CD8+, and natural killer (NK) cell counts using the current standard protocol.[12] The PHQ-9 was utilized to screen the patients for depression symptoms experienced over the past 2 weeks. The investigated items included anhedonia, depressed mood, sleep disturbances, fatigue, appetite changes, low self-esteem, concentration problems, psychomotor disturbances, and suicidal ideation. The responses were rated on a 4-point Likert scale from 0 (not at all) to 3 (almost every day), yielding a total score of 27. Higher scores indicated more severe symptoms, with scores of 0–4 corresponding to no depression, 5–9 to mild depression, 10–14 to moderate depression, 15–19 to moderately severe depression, and 20-27 to severe depression.[13] The GAD-7 was employed to screen the severity of anxiety symptoms over the last 2 weeks and comprised 7 questions. The patients rated their levels of agreement with several statements on a 4-point

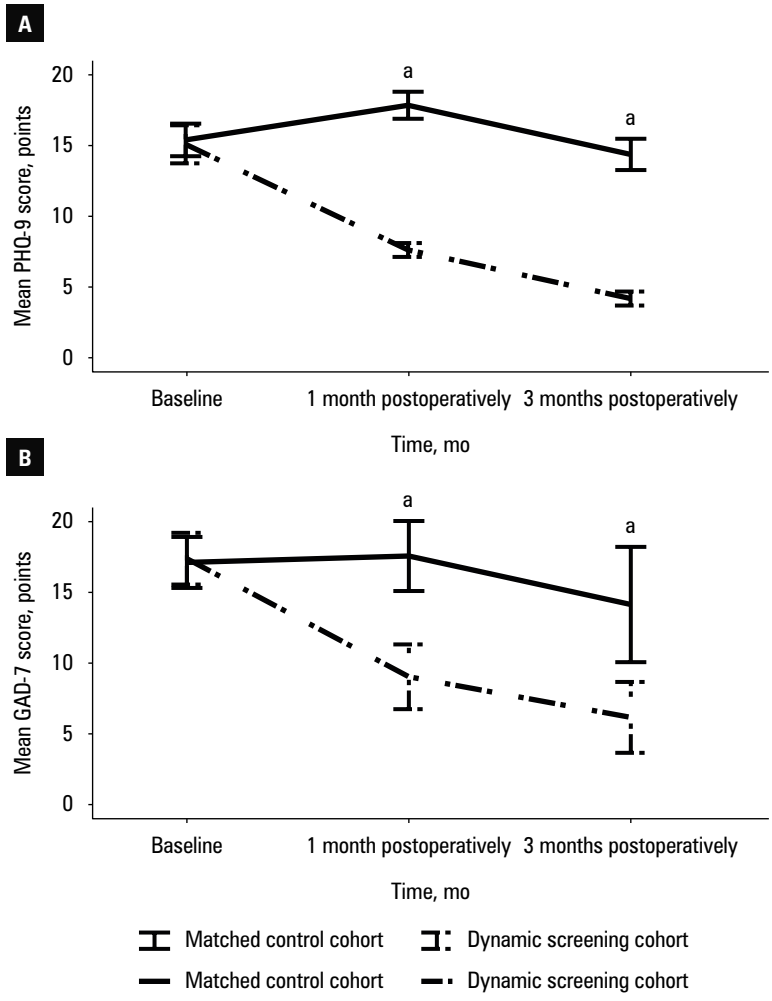

FIGURE 2 Comparison of mean Patient Health Questionnaire-9 (PHQ-9; **A**) and Generalized Anxiety Disorder-7 (GAD-7; **B**) scores before surgery and at 1- and 3-month follow-up between the dynamic screening and matched control cohorts

a $P < 0.05$ between the cohorts

Likert scale (where 0 meant "not at all" and 3 "almost every day"). The total score was 21, with higher scores indicating greater symptom severity: a score of 0–4 indicated no anxiety, 5–9 corresponded to mild anxiety, 10–14 meant moderate anxiety, and 15–21 severe anxiety.[14] Health-related QoL was assessed using the 5-level European Quality of Life Five-dimension (EQ-5D-5L) questionnaire, which included 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. The responses were scored on a 5-point Likert scale ranging from "no problems" to "extreme problems."[15] Disease-free survival (DFS) was defined as the interval from surgery to the first occurrence of local progression, distant progression, biochemical failure, or death from all causes. Adverse events associated with psychotherapy or pharmacological treatments for anxiety and depression were also recorded.

The primary end point was to compare the 1-year DFS from all-cause local progression, distant progression, biochemical failure, or death between the 2 cohorts. Secondary outcomes included immune function, anxiety and depression scores, and EQ-5D-5L scores within 3 months after surgery.

Statistical analysis The sample size was calculated using PASS statistical software, version 19.0 (NCSS, LLC, Kaysville, Utah, United States). According to previous research, 1-year DFS in patients undergoing surgery for gastric or colorectal cancers ranged from 84% to 86%.[16,17] Based on a multidisciplinary expert consensus derived from a series of case discussions, the true survival proportion of patients undergoing dynamic screening was over 90%. To achieve 90% power with a 2-sided type I error rate of 5%, 352 cases per cohort were required to detect a difference of 10%. Accounting for a 20% loss to data, the final sample size was set at 440 per cohort.

SPSS software, version 22.0 (IBM Corp., Armonk, New York, United States) was used for statistical analysis. Significance was set at a P value below 0.05. The Kolmogorov–Smirnov test was employed to assess data normality. Normally distributed data, non-normally distributed data, and categorical data were reported as mean (SD), median (interquartile range [IQR]), and percentage, respectively. The differences between the cohorts were compared using the t test, the Mann–Whitney test, and the χ^2 test, respectively. Repeated measures mixed-design analysis of variance (rm-ANOVA) was used to compare the repeatedly measured data between the cohorts, followed by the Bonferroni correction (an adjusted significance level of 0.05/3 = 0.017). Kaplan–Meier curves were used to compare the probability of survival, and the log-rank test was applied to compare differences between the cohorts.

Ethics Ethical approval for this study was provided by the institutional Research Ethics Board (*-Y-2025098) in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants upon enrollment.

RESULTS The flow chart of the study cohorts is presented in **FIGURE 1**, and **TABLE 1** outlines the demographic and clinical characteristics of the participants. The baseline characteristics of the patients, including the covariates used for the PSM, were well balanced between the dynamic screening and the control cohorts ($P > 0.05$).

After dynamic screening for anxiety and depression, the proportion of the patients receiving supportive psychotherapy, cognitive behavioral therapy, mindfulness-based therapy, and psychopharmacological therapy was 7.8%, 10.4%, 11.2%, and 12.7%, respectively. As illustrated in **FIGURE 2**, the levels of anxiety and depression were comparable at baseline prior to surgery between both cohorts, with mean (SD) PHQ-9 scores of 15.61 (3.19) vs 15.31 (3.62) points ($P = 0.72$) and mean (SD) GAD-7 scores of 15.3 (3.17) vs 15.69 (3.14) points ($P = 0.74$). Furthermore, the average PHQ-9 scores declined ($P < 0.001$) over time

TABLE 1 Comparison of demographic and clinical characteristics of the patients undergoing primary surgery for gastrointestinal cancers

Variable		Dynamic screening cohort (n = 384)	Matched control cohort (n = 384)	*P* value
Age, y		65.07 (8.51)	66.03 (9.29)	0.64
Sex	Men	185 (48.2)	173 (45.1)	0.43
	Women	199 (51.8)	211 (54.9)	
Ethnicity	Han Chinese	284 (74)	288 (75)	0.8
	Other	100 (26)	96 (25)	
BMI, kg/m^2		22.58 (3.12)	22.612 (2.53)	0.96
Type of primary tumor	Upper GI cancer	149 (38.8)	153 (39.8)	0.83
	Lower GI cancer	235 (61.2)	231 (60.2)	
Disease duration, mo		7.9 (3.12)	7.62 (3.81)	0.53
TMN stage	I	46 (12.)	48 (12.5)	0.88
	II	157 (40.9)	162 (42.2)	
	III	181 (47.1)	174 (45.3)	
ASA class	I	9 (2.3)	8 (2.1)	0.9
	II	140 (36.3)	130 (33.9)	
	III	226 (58.5)	234 (60.9)	
	IV	11 (2.8)	12 (3.1)	
Type of surgery	Open surgery	122 (31.8)	117 (30.5)	0.76
	Laparoscopic surgery	262 (68.2)	267 (69.5)	
Adjunctive radiotherapy/chemotherapy	No	111 (28.9)	124 (32.3)	0.35
	Yes	273 (71.1)	260 (67.7)	
Number of comorbidities, median (IQR)		1 (0–2)	1 (0–2)	0.63
Inflammatory cytokines, pg/ml	IL-6	13.17 (5.06)	12.99 (1.36)	0.46
	TNF-α	9.79 (1.21)	9.47 (1.11)	0.51
Leukocyte count, × 10^9/l	CD3+	57.25 (2.62)	58.77 (4.19)	0.3
	CD4+	32.67 (3.87)	31.50 (4.04)	0.49
	CD8+	26.63 (3.4)	25.19 (3.13)	0.31
	NK cells	24.33 (4.34)	24.27 (4.86)	0.98
PHQ-9 score, points	No depression (0–4)	314 (71.7)	309 (70.5)	0.91
	Mild depression (5–9)	65 (14.8)	68 (15.5)	
	Moderate depression (10–14)	34 (7.8)	30 (6.8)	
	Moderately severe depression (15–19)	17 (3.9)	21 (4.8)	
	Severe depression (20–27)	8 (1.8)	10 (2.3)	
GAD-7 score, points	No anxiety (0–4)	343 (78.3)	340 (77.6)	0.97
	Mild anxiety (5–9)	46 (10.5)	47 (10.7)	
	Moderate anxiety (10–14)	34 (7.8)	33 (7.3)	
	Severe anxiety (15–21)	15 (3.4)	19 (4.3)	

Data are presented as number (percentage) or mean (SD) unless indicated otherwise.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; GAD-7, Generalized Anxiety Disorder-7 item; IL, interleukin; IQR, interquartile range; NK, natural killer; PHQ-9, Patient Health Questionnaire-9; TNF-α, tumor necrosis factor α; TNM, tumor-node-metastasis

in a direct comparison to the baseline value in the patients undergoing dynamic screening for anxiety and depression. In contrast, the matched control cohort's PHQ-9 scores tended to increase during follow-up. According to the rm-ANOVA analysis, mean (SD) PHQ-9 scores in the dynamic screening cohort were 8.19 (1.32) and 6.91 (1.33) points at 1- and 3-month follow-up, respectively, and they were markedly lower than those in the matched control cohort (mean [SD], 17.95 [2.69] and 16.64 [3.12] points; P <0.001). Similar findings were observed for the GAD-7 scores, with the patients in the dynamic screening cohort exhibiting lower mean (SD) scores 1 and 3 months after surgery, as compared with the matched controls (7.73 [3.94) vs 15.87 [4.26] points at 1 month and 5.01 [3.31] vs 12.62 [4.81] points 3 months postoperatively; P <0.001).

FIGURE 3 illustrates a comparison of immune function in both groups. Considerable differences were observed in mean (SD) CD3+ counts (61.25 [7.04] vs 52.27 [4.7]; P <0.001), CD4+/CD8+ ratio (1.67 [0.39] vs 1.39 [0.14]; P = 0.046), and NK cell counts (21.96 [1.79] vs 25.19 [3.13];

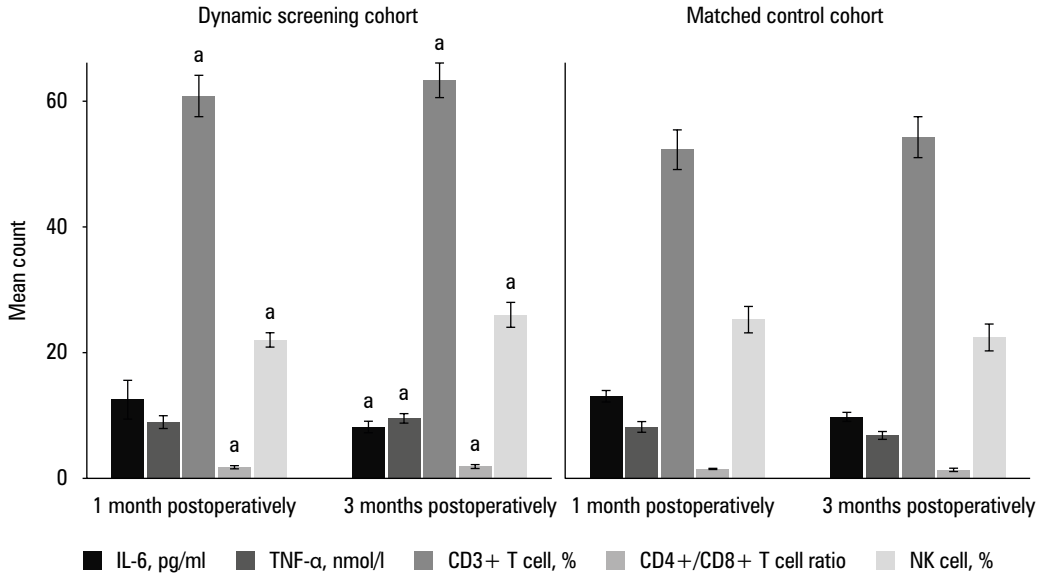

FIGURE 3 Comparison of inflammatory cytokine and leukocyte counts between the dynamic screening and matched control cohorts

a $P < 0.05$ between the cohorts

Abbreviations: see **TABLE 1**

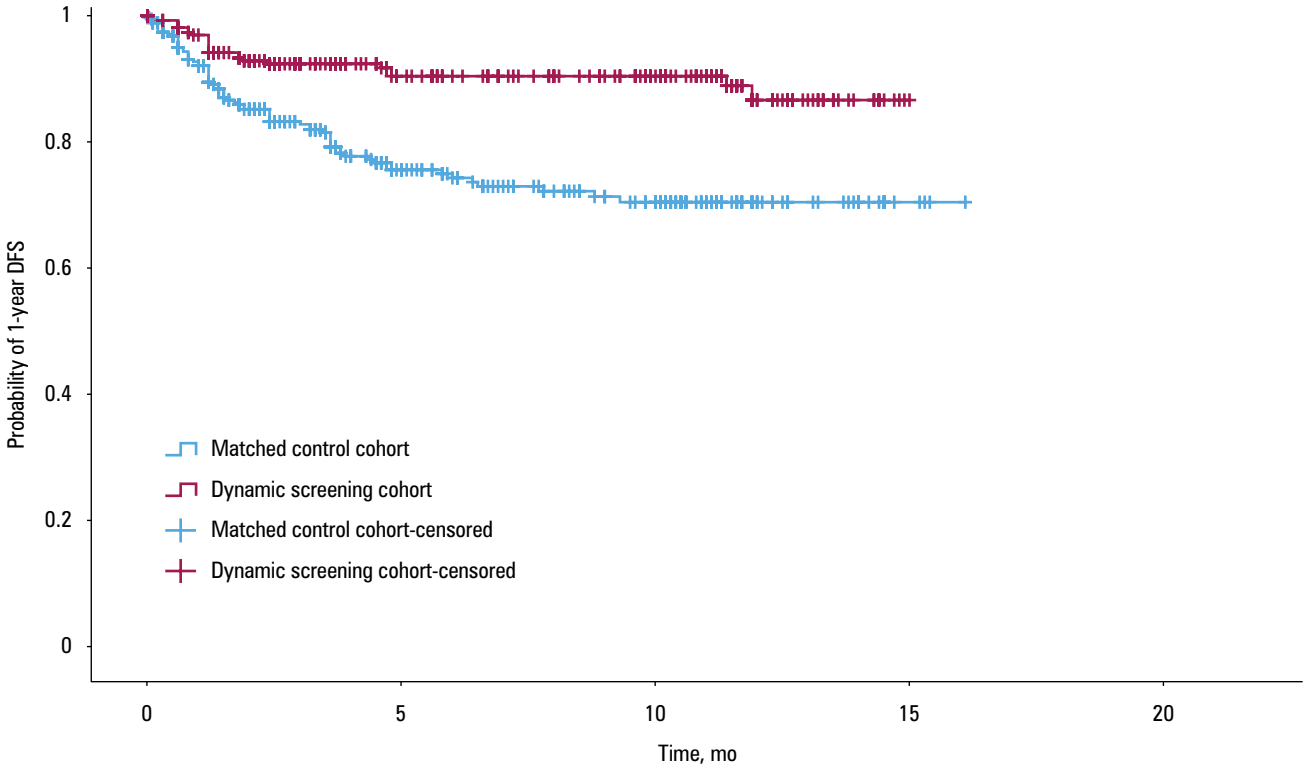

FIGURE 4 Kaplan–Meier survival curves for the patients who received dynamic screening for anxiety and depression in comparison with the matched control cohort without screening at 1-year follow-up

Abbreviations: DFS, disease-free survival

$P = 0.006$) between the screening and the control cohorts 1 month after the operation. At 3-month follow-up, marked differences were found between the 2 groups in terms of inflammatory cytokine levels, including the interleukin-6 (IL-6; 8.08 [1.44] vs 9.7 [1.07]; $P = 0.005$) and tumor necrosis factor α (TNF-α; 9.74 [0.73] vs 6.71 [0.89]; $P < 0.001$) levels. Moreover, the leukocyte counts, specifically the CD3+ count (63.33 [4.34] vs 54.27 [4.86]; $P < 0.001$), CD4+/CD8+ ratio (1.77 [0.49] vs 1.25 [0.39]; $P = 0.009$), and the NK cell count (25.96 [3.12] vs 22.35 [3.18]; $P = 0.01$) remained different between the 2 cohorts.

Median (IQR) observation time was 12 (9–15) months. According to the Kaplan–Meier survival curves, 91.4% of the patients in the dynamic screening cohort reported DFS within 1-year follow-up, as compared with 81.2% of the matched control group. Furthermore, the patients who underwent dynamic screening for anxiety and depression had longer DFS time of 13.55 (95% CI, 13.01–14.09) months, as opposed to

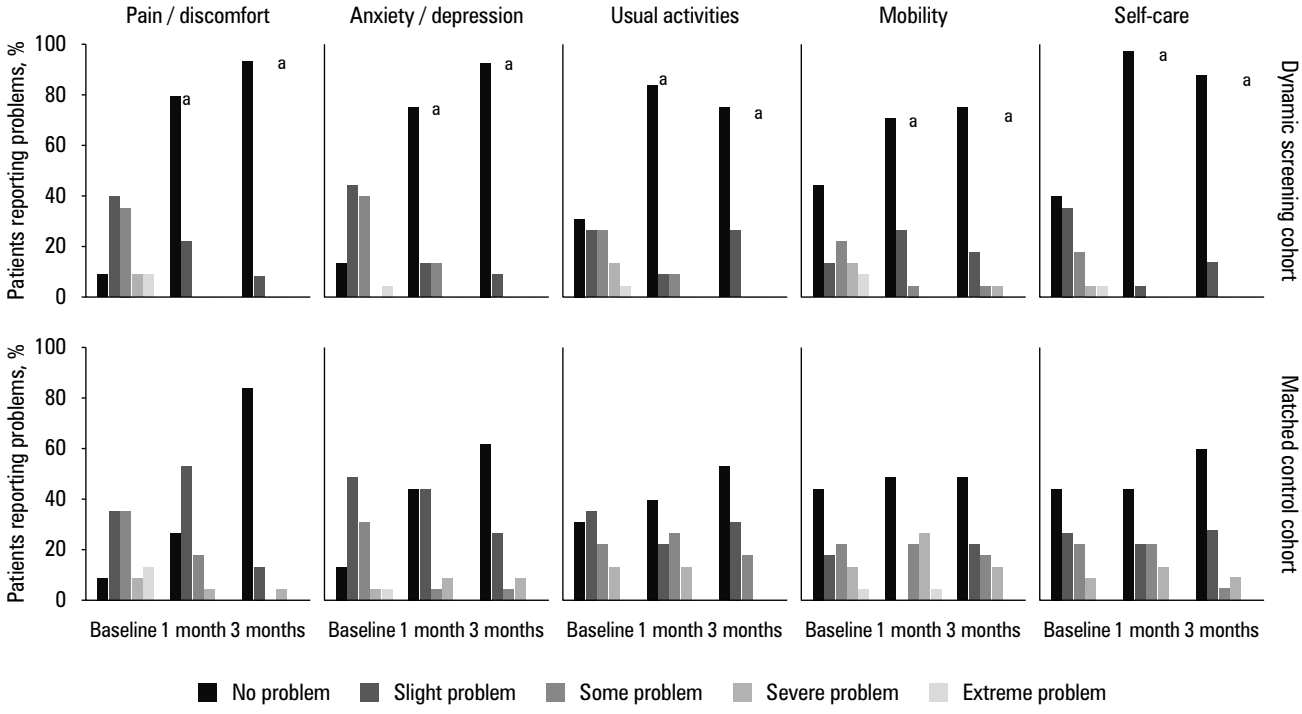

FIGURE 5 The proportion of patients reporting problems in the 5 domains of the 5-level European Quality of Life Five-dimension questionnaire across all time points before and after primary surgery for gastrointestinal cancer

a $P < 0.05$ between the cohorts

10.29 (95% CI, 9.52–11.06) months for those who did not (log-rank test; $P < 0.001$; **FIGURE 4**).

In comparison with their baseline EQ-5D-5L scores, the patients in both cohorts showed great improvements during follow-up. However, the differences in the percentage of patients reporting no problems across all 5 dimensions between the 2 groups were significant at both follow-up time points ($P < 0.001$; **FIGURE 5**).

No serious complications related to nonpharmacological and pharmacological treatments for anxiety and depression were observed in the screening cohort. Minor complications, including nausea, vomiting, dizziness, sleepiness, and tremors, were reported in 8.2% of the screened patients.

DISCUSSION Our study found that time-dynamic screening for anxiety and depression combined with psychological treatment was associated with improved survival outcomes in the patients undergoing primary surgery for GI caners. It significantly reduced the severity of anxiety and depression symptoms, resulting in better postoperative immune function and higher health-related QoL, as compared with the matched control patients.

Prior research showed that immune cells could release proinflammatory cytokines, including ILs and TNFs, in response to GI cancers or cancer-related therapies, which acted on the brain and contributed to the onset of anxiety and depression symptoms.[18] Conversely, anxiety and depression symptoms activated the hypothalamic-pituitary-adrenal axis, leading to disturbances in cortisol and adrenal function, which in turn caused increased cytokine production and impaired immune function.[19] A prior systematic review and meta-analysis showed that inflammatory cytokine levels were significantly associated with depressive symptoms, with a standardized mean difference (MD) of 0.59 with I^2 of 57.9% for IL-6, and MD of 0.73 with I^2 of 74.1% for TNF-α.[20] Consistent with earlier data, our results showed that IL-6 and TNF-α levels significantly decreased over time in the dynamic screening cohort, as compared with the controls, at 3-month follow-up. These changes can be attributed to the marked reductions in the PHQ-9 and GAD-7 scores in this cohort, as opposed to the matched controls ($P < 0.001$). Moreover, notable differences were observed between the 2 groups in the CD3+ counts, CD4+/CD8+ ratio, and NK cell counts at all follow-up time points, indicating improved immune function in the patients with lower levels of anxiety and depression who underwent time-dynamic screening, in comparison with those who did not ($P < 0.001$). In addition to our findings, a previous randomized controlled trial (RCT) investigating psychological interventions for gastric cancer patients showed that the intervention group exhibited significant reductions in anxiety (Hospital Anxiety and Depression Scale [HADS] scores decreased from 12.3 to 7.1 points) and depression levels (HADS scores dropped from 11.8 to 6.5 points). This was accompanied by improved immune function, indicated by a CD4+/CD8+ ratio of 1.44 ($P = 0.001$) and reduced inflammatory markers, with IL-6 levels decreasing from 12.4 to 8.2 pg/ml ($P = 0.001$), and TNF-α levels declining from 9.3 to 6.1 pg/ml ($P = 0.003$).[21]

Although cancer characteristics are immutable factors associated with reduced survival rate in patients with GI cancers, preoperative anxiety and depression are identified as predictors of all-cause mortality.[22] A recent prospective trial involving older adults with GI cancers reported that the 12-month overall survival rate was 50% among the patients experiencing anxiety / depression according to Kaplan–Meier curves.[23] Another study indicated that individuals with postoperative anxiety and depression had worse prognoses, as DFS was significantly shorter in depressed than nondepressed patients during 36-month follow--up in gastric cancer cases, with a hazard ratio (HR) of 2.129 (95% CI, 1.061–4.273).[24] Chronic stress caused by anxiety and depression activated the sympathetic nervous system and promoted the release of neurotransmitters, particularly catecholamines, which could accelerate cancer proliferation, migration and metastasis through β2-adrenergic receptors pathways, and epithelial--mesenchymal transition.[25] In addition to hormonal factors, anxiety and depression also suppressed the function of NK cells and DNA repair enzymes, both of which play an important role in cancer defense.[26]

The patients experiencing symptoms of anxiety and depression were reported to have lower treatment adherence. These individuals underwent significantly fewer adjunctive chemotherapy sessions (an average of 10.3 [95% CI, 9.1–11.4]) and were less likely to receive radiotherapy than the general population (1.6% vs 3.9%; P <0.05). This resulted in a poor prognosis, with an increased risk of all-cause mortality (HR, 1.96; 95% CI, 1.67–2.31), which was suggested as one of the potential mechanisms proposed in previous studies.[27] Consequently, our results showed that the percentage of patients reporting 1-year survival from GI cancer prognosis was considerably higher in the screening cohort, which also exhibited lower anxiety and depression levels than the matched controls. Additionally, these patients had longer DFS than the control group at 1-year follow-up (P <0.001). Consistent with our findings, the 2-year DFS rate was also improved in the gastric patients who received effective psychological interventions after surgery, as compared with the controls (81.2% vs 68.5%; P = 0.005).[21]

QoL is a major concern for cancer patients; however, higher levels of anxiety and depression have been associated with decreased QoL among stage I–III GI cancer survivors.[28] A recent cross--sectional study reported that anxiety and depression adversely impacted patients' physical activity and functional status, leading to poor QoL in individuals with colorectal cancer (P = 0.02 for anxiety and P <0.001 for depression).[29] Conversely, both pharmacological and nonpharmacological interventions were shown to reduce anxiety and depression levels and improve QoL scores in colorectal cancers patients in a meta-analysis of 3438 patients across 13 RCTs.[30] Nevertheless, optimal management of anxiety and depression in cancer survivors should be provided by appropriately trained psychologists according to the American Society of Clinical Oncology guidelines.[31] As a result, the current study found that the screening cohort experienced considerably greater improvement in QoL, indicated by better EQ-5D-5L scores within 3 months after surgery, as compared with the control cohort. This improvement might be attributed to the regular reassessment of the patients' status, which allowed for timely referrals to psychologists for treatment modifications targeting anxiety and depression.

This study had several limitations. First, numerous confounding factors influencing the patients' DFS, such as differences in disease biology, might be present. Second, the retrospective design could introduce confounding bias. Third, conducting the study at a single center restricted its generalizability to the broader population of patients with GI cancers. Finally, the follow-up was limited to 1 year, preventing the analysis of long--term outcomes over 3 to 5 years, which are typical in GI cancers and would strengthen the clinical significance of the study. In the future, a well--designed RCT is needed to confirm our findings.

CONCLUSIONS Time-dynamic screening with subsequent interventions effectively reduced the patients' anxiety and depression levels, enhanced postoperative immune function, and improved QoL, contributing to better DFS over 1-year follow-up in patients undergoing primary surgery for GI cancers. Therefore, it is recommended to incorporate dynamic screening as part of routine perioperative care for these patients.

ARTICLE INFORMATION

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CONTRIBUTIONS STATEMENT LZ was involved in the conception and design, analysis and interpretation of the data, drafting of the paper, revising it critically for intellectual content, and the final approval of the version to be published. TS was involved in the conception and design, analysis and interpretation of the data, drafting of the paper, and revising it critically for intellectual content. LG, WH, and MZ were involved in the conception and design, analysis and interpretation of the data, and drafting of the paper. All authors read and approved the final version of the manuscript.

AI STATEMENT Artificial intelligence was not used in the preparation of this manuscript.

CONFLICTS OF INTEREST None declared.

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