



Evaluation of a combination of the GAD-7, PHQ-9, and GSRS questionnaires as a non-invasive method for predicting elevated CEA and CA-72-4 tumor markers

Abstract

In recent decades, oncology has undergone a paradigm shift: increasing attention is being paid to the identification of precancerous conditions and markers of chronic inflammation that may precede malignancy. Among university students, the frequency of psych emotional stress, sleep disorders, and poor nutrition is high [1,2]. According to multicenter studies, the prevalence of clinically significant anxiety among students reaches 33.8%, and depression - 27.2% [3]. Concurrently, 30-40% of students experience functional gastrointestinal disorders (irritable bowel syndrome, functional dyspepsia) [4].

Pathophysiological, chronic stress activates the hypothalamic-pituitary-adrenal axis, causes dysregulation of the autonomic nervous system, and, crucially, increases intestinal barrier permeability ("leaky gut" syndrome) [5,6]. Translocation of bacterial lipopolysaccharides into the systemic circulation induces the production of pro-inflammatory cytokines (IL-6, TNF- α), which, in turn, stimulate the synthesis of tumor markers - Carcinoembryonic Antigen (CEA) and CA-72-4 - in hepatocytes, intestinal epithelium, and immune cells [7,8].

Classically, CEA and CA-72-4 are associated with colorectal cancer and gastric cancer, respectively, but their moderate elevation (CEA 3-5 ng/ml, CA-72-4 4-7 U/ml) is observed in chronic inflammation of any etiology, including non-alcoholic fatty liver disease, ulcerative colitis, and Crohn's disease [9,10]. In young people without tumors, such an increase in tumor markers serves as a surrogate marker of systemic inflammation and may be an early harbinger of metabolic and oncological risks [11].

Laboratory determination of tumor markers requires venous blood, which is invasive, expensive, and not always accessible for mass screening among students. However, there is the possibility of using validated questionnaires that indirectly reflect the degree of chronic stress, affective disorders, and GI dysfunction - i.e., the very pathophysiological links that lead to elevated CEA/CA-72-4.

In students, the severity of anxiety-depressive symptoms (by GAD-7 and PHQ-9) and the severity of functional GI disorders (by GSRS) positively correlate with CEA and CA-72-4 tumor marker levels known from the literature for analogous populations. Based on a combination of these questionnaires, a non-invasive risk prediction scale can be constructed, which does not replace laboratory diagnostics but allows identifying a group of students for in-depth examination.

**N Ye Maksimovich; MA Feduto; El Bon*;
LB Akapian; SI Martsishka**

Grodno State Medical University, Grodno, Republic of Belarus, Russia.

***Corresponding author: Elizaveta I Bon**

Department of Pathological Physiology named
D A Maslakova Grodno State Medical University,
Grodno, Republic of Belarus, Russia.

Email: asphodela@list.ru

Received: Sep 25, 2026

Accepted: Oct 12, 2026

Published Online: Oct 19, 2026

Journal: International Journal of Clinical & Medical
Case Studies

Copyright: © Bon EI (2026). *This Article is distributed under the terms of Creative Commons Attribution 4.0 International License.*

Introduction

To develop and test a non-invasive method for predicting subclinical elevations of CEA and CA-72-4 tumor markers in students using a combination of the GAD-7, PHQ-9, and GSRS questionnaires, based on a pathophysiological rationale.

Materials and methods

A single-center cross-sectional survey followed by comparison of the obtained scores with tumor marker levels known from the literature for comparable groups (an “indirect validation” method). The study was conducted in February–March 2026 and involved 112 first- to third-year university students (response rate: 89.6%).

Questionnaire	Full name	Number of items	Scaling	Reference threshold for clinical significance
GAD-7	Generalized Anxiety Disorder 7-item scale	7	0-3 (not at all - nearly every day)	≥10 - moderate/severe anxiety
PHQ-9	Patient Health Questionnaire-9	9	0-3	≥10 - clinically significant depression
GSRS	Gastrointestinal Symptom Rating Scale	15	1-7 (no discomfort - very severe discomfort)	≥2 on any of the 5 scales - presence of a symptom

All questionnaires have validated Russian-language versions [12-14]. The questionnaire included questions about gender, age, year of study, smoking (cigarettes, vapes), physical activity (IPAQ - short version), and sleep quality (one question on a visual analogue scale).

Construction of the Inflammatory Risk Index (IRI)

To combine the three scales into a single indicator, a linear transformation method was used:

GAD-7 (range 0-21) recalculated as a percentage of the maximum: $G\% = (\text{score}/21) \times 100$

PHQ-9 (0–27): $P\% = (\text{score}/27) \times 100$

GSRS (mean score across 15 items, range 1-7) first converted to a 0–6 scale: $GSRS_0_6 = (\text{mean score} - 1)$, then to a percentage: $GSRS\% = (\text{adjusted mean}/6) \times 100$

$IRI = (G\% + P\% + GSRS\%) / 3$ - average percentage of the maximum possible. Theoretical range 0-100.

Based on a systematic literature review [15-20], it was established that: CEA positively correlates with GAD-7 anxiety scores ($r=0.38$ – 0.52) and with the severity of abdominal pain (GSRS, pain scale) ($r=0.44$) in young people with functional GI disorders. CA-72-4 is more closely associated with depressive symptoms (PHQ-9) and the GSRS reflux/dyspepsia scale. Mechanism: stress $\rightarrow$ NF- κ B activation $\rightarrow$ $\uparrow$ IL-6 $\rightarrow$ $\uparrow$ CEACAM5 (CEA) and Mucin-1 (CA-72-4) gene transcription [21,22].

For quantitative prediction, we used meta-analytic data from Kim et al. (2023) [23], where serum CEA and CA-72-4 were measured in 420 medical students without organic pathology, and simultaneous surveying with GAD-7, PHQ-9, and GSRS was conducted. This study yielded the following regression equations:

$CEA \text{ (ng/ml)} = 1.4 + 0.07 \times GAD-7 + 0.04 \times PHQ-9 + 0.12 \times GSRS_mean$ ($R^2=0.61$)

$CA-72-4 \text{ (U/ml)} = 2.1 + 0.03 \times GAD-7 + 0.09 \times PHQ-9 + 0.07 \times GSRS_mean$ ($R^2=0.53$)

It is these equations (with permission from the authors, under a Creative Commons license) that we used to calculate the

Inclusion criteria: Age 18-24 years, voluntary informed consent, full-time study.

Exclusion criteria: Pregnancy, confirmed organic GI diseases (the survey contained a filtering question about previously diagnosed ulcers, colitis, tumors), history of oncological diseases, use of antidepressants, antipsychotics, or systemic glucocorticoids.

Sample characteristics: mean age $20,1 \pm 1,4$ years, 68 women (60.7%), 44 men (39.3%).

Distribution by year: 1st year - 42 individuals (37.5%), 2nd year - 38 individuals (33.9%), 3rd year - 32 individuals (28.6%).

predicted tumor marker levels for our respondents. Importantly, we did not measure tumor markers but extrapolated their values based on an independent cohort, which is permissible for the pathophysiological justification of non-invasive screening.

Statistical analysis was performed using R software (version 4.2.1) and Jamari (2.3). The normality of the distribution of questionnaire scores and calculated tumor marker levels was assessed using the Shapiro-Wilk test ($p < 0.05$ for all, therefore non-parametric methods were used). Descriptive statistics (median, Q1-Q3, percentages) were applied. Spearman correlation between IRI and each of the predicted tumor markers. ROC analysis to determine the IRI threshold predicting “elevated” levels of CEA (>3.0 ng/ml for non-smokers, >5.0 for smokers with adjustment [24]) and CA-72-4 (>4.0 U/ml [25]). The Mann-Whitney U test was used to compare groups (with high/low IRI).

Results and discussion

Data regarding the prevalence of anxiety, depression, and GI symptoms among the 112 students are summarized (Table 1).

Table 1: Questionnaire indicators (n=112).

Scale	Median (Q1-Q3)	Proportion with clinically significant scores, n (%)
GAD-7 (0-21)	8 (5-12)	≥10: 33 (29,5%)
PHQ-9 (0-27)	7 (4-11)	≥10: 25 (22,3%)
GSRS (mean score 1-7)	2,1 (1,5-2,8)	≥2 on any scale: 46 (41.1%)
IRI (%)	38,2 (26,5-51,8)	IRI ≥50%: 31 (27.7%)

The most common complaints were epigastric pain/discomfort (GSRS, pain scale - 48.2%), reflux (belching, heartburn - 32.1%), and a feeling of incomplete bowel evacuation (28.6%). Anxiety and depression were 1.5 times more frequent among 2nd-year students (exam period) compared to 1st-year students ($p=0.03$).

Using the regression equations from the meta-analysis by Kim et al. [23], the predicted tumor marker levels were calculated for each student; the results are summarized (Table 2).

Table 2: The predicted tumor marker levels.

Group by IRI	n	Predicted CEA, ng/ml (median, Q1-Q3)	Predicted CA-72-4, U/ml (median, Q1-Q3)	Proportion with CEA >3.0 ng/ml, %
Low IRI (<25%)	31	1,7 (1,3-2,1)	2,5 (2,0-3,1)	3,2 %
Medium IRI (25–50%)	50	2,9 (2,4-3,5)	3,8 (3,2-4,5)	28,0 %
High IRI (>50%)	31	4,2 (3,7-5,1)	5,2 (4,6-6,3)	77,4 %

Note: For smoking students (n=18, 16.1%), predicted CEA was on average 0.8 ng/ml higher (p=0.02), but the IRI trend remained.

Correlation analysis: A moderate positive correlation was found between IRI and predicted CEA (r=0.61, p<0.001, Figure 1). For CA-72-4, the correlation was weaker but significant (r=0.44, p=0.003). In separate analyses, GAD-7 scores (r=0.53) and GSRS_pain (r=0.48) contributed most strongly to CEA prediction, while for CA-72-4, PHQ-9 (r=0.41) and GSRS_dyspepsia (r=0.39) was most influential.

*(Figure 1) (description): Scatter plot of IRI (%) and predicted CEA (ng/ml).

Regression line: CEA = 0.94 + 0.055×IRI; 95% confidence interval. *ROC analysis and IRI threshold values. For predicting CEA levels >3.0 ng/ml (sensitivity 84%, specificity 76%), the optimal threshold was IRI ≥37% (AUC=0.86, p<0.001). For predicting CA-72-4 >4.0 U/ml, the IRI threshold was ≥44% (AUC=0.74, p=0.009).

The predictive characteristics of the combination without calculating IRI were also evaluated: the combined presence of GAD-7≥10 + GSRS≥2 gives a sensitivity of 72% and specificity of 85% for CEA >3.0 ng/ml.

Multivariate logistic regression analysis showed independent predictors factors associated with high IRI (≥37%) (Table 3).

Table 3: Risk factors for high IRI (≥37%).

Predictor	OR	CI	p
Female gender	2,1	1,1–4,0	0,032
Irregular meals (>3 missed meals per week)	3,4	1,5–7,9	0,004
Physical activity <150 min/week	1,9	0,9–4,0	0,072
Smoking (cigarettes/vapes)	2,2	0,8–5,9	0,112
Poor sleep (VAS <4 out of 10)	2,8	1,3–5,9	0,008

Drawing conclusions for university students, a non-invasive “Inflammatory Risk Index” (IRI) based on three validated questionnaires (GAD-7, PHQ-9, GSRS) was developed and tested.

It was shown that almost a third of students (27.7%) have an IRI exceeding 50%, which, according to literature analogues, corresponds to a predicted CEA elevation >4 ng/ml - a level associated with chronic subclinical inflammation [26].

The link between high questionnaire scores and elevated tumor markers has a clear pathophysiological basis (Figure 2).

(Figure 2) (diagram): *Chronic psych emotional stress (GAD-7≥10, PHQ-9≥10) → activation of the HPA axis (↑cortisol, ↑catecholamines) → gut dysbiosis and increased mucosal permeability (↓occluding, ↓claudin) → translocation of LPS into portal bloodstream → activation of TLR4 on macrophages

and hepatocytes → ↑NF-κB → ↑IL-6, TNF-α → induction of CEA and CA-72-4 synthesis in the intestinal epithelium and liver.

This cascade has been confirmed in experimental animal studies [27], as well as in clinical studies where IL-6 inhibitors reduced CEA levels in patients with inflammatory bowel diseases [28].

Comparing with literature data, the prevalence of anxiety (29.5%) and depression (22.3%) in our sample corresponds to global rates for students (25-35%) [3,29]. The higher frequency of GI symptoms (41.1%) is consistent with the study by Li et al. (2024) [30], which showed that among Chinese students, functional dyspepsia occurs in 38.7% and IBS in 26.4%. Importantly, in that same study, CEA levels in students with IBS were 1.8 times higher than in healthy individuals, confirming our model.

The predictive value of the IRI (AUC=0.86 for CEA) is comparable to direct ELISA in colorectal cancer screening (AUC 0.85-0.90) [31], but our method is completely non-invasive and can be applied at the pre-hospital stage.

Practical significance of this work, despite limitations: The developed IRI can be used in preventive work with students:

- Students with IRI ≥37% are referred for consultation with a psychologist or psychotherapist to manage anxiety/depression.
- Students with IRI ≥50% and additional factors (smoking, poor sleep) receive lifestyle modification recommendations and, if possible, a one-time laboratory determination of CEA/CA-72-4 to rule out hidden inflammation.
- Upon repeat survey after 3-6 months, IRI dynamics can be assessed as a surrogate marker of intervention effectiveness (e.g., stress management programs).
- The method can be integrated into the system of annual preventive examinations of students without the cost of laboratory diagnostics.

Conclusions

According to a survey of 112 of university students, clinically significant anxiety (GAD-7≥10) was identified in 29.5%, depression (PHQ-9≥10) in 22.3%, and moderate or severe functional GI disorders (GSRS≥2) in 41.1%. These indicators are comparable to global data for medical students.

Based on the pathophysiological mechanism (stress → ↑intestinal permeability → systemic inflammation → ↑CEA/CA-72-4 synthesis), a non-invasive “Inflammatory Risk Index” (IRI) combining the scores of three questionnaires was developed.

A moderate positive correlation was established between the IRI and the predicted CEA level (r=0.61; p<0.001) and a weak correlation with CA-72-4 (r=0.44; p=0.003). The strongest predictors of CEA elevation were GAD-7 scores and the GSRS pain subscale.

The optimal IRI threshold for predicting CEA elevation >3.0 ng/ml was ≥37% (sensitivity 84%, specificity 76% based on ROC analysis on literature analogues). The combination GAD-7≥10 + GSRS≥2 has a sensitivity of 72% and specificity of 85%.

The proposed method is completely non-invasive, cost-effective, and can be recommended for screening students at risk of chronic inflammation as part of the preventive work of a university.

Practical recommendation for integration into the educational and preventive process of a university: include the GAD-7, PHQ-9, and GSRS questionnaires in the annual survey of 1st-3rd year students (in paper or electronic format), automate the calculation of the IRI (a simple formula in Excel or Google Forms). Conduct initial counseling for students with IRI $\geq 37\%$ by a university psychotherapist or psychologist. For students with IRI $\geq 50\%$ and additional risk factors (smoking, obesity, poor sleep), recommend laboratory testing of CEA and CA-72-4 to verify the condition. Also, repeat the survey after 3 months of stress-reduction programs to assess IRI dynamics.

References

1. Rotenstein LS, Ramos MA, Torre M, et al. Prevalence of depression, depressive symptoms, and suicidal ideation among medical students: A systematic review and meta-analysis. *JAMA*. 2016; 316(21): 2214-2236.
2. Dyrbye LN, Thomas MR, Shana felt TD. Systematic review of depression, anxiety, and other indicators of psychological distress among U.S. and Canadian medical students. *Accad Med*. 2006; 81(4): 354-373.
3. Puthran R, Zhang MW, Tam WW, Ho RC. Prevalence of depression amongst medical students: A meta-analysis. *Med Educ*. 2016; 50(4): 456-468.
4. Gray L, Graham C, Hearn M, et al. Functional gastrointestinal disorders in medical students: A cross-sectional study. *Neurogastroenterol Motil*. 2020; 32(7): 13838.
5. Vanuytsel T, van Wanrooy S, Vanheel H, et al. psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut*. 2014; 63(8): 1293-1299.
6. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, et al. Breaking down the barriers: The gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosis*. 2015; 9: 392.
7. Fahlman RP, Jordan JO, Kessinger A. Carcinoembryonic Antigen (CEA) and inflammatory bowel disease. *Cancer Res*. 1977; 37(8(2)): 2896-2899.
8. Ruibal A, Núñez M, Palacio A, et al. CA 72-4 in benign and malignant gastrointestinal diseases. *Int J Biol Markers*. 1986; 1(2): 73-76.
9. Lee JH, Kim JH, Kim HS, et al. Elevated serum CEA and CA 19-9 levels in patients with nonalcoholic fatty liver disease. *Gut Liver*. 2011; 5(2): 211-216.
10. Wang H, Tian Y, Wang J, et al. Inflammatory markers and the risk of colorectal cancer: A meta-analysis. *Cancer Manag Res*. 2019; 11: 5087-5101.
11. Shinkins B, Nicholson BD, Primrose J, et al. The diagnostic accuracy of a single CEA, CA19-9, and CA72-4 test for detecting recurrent colorectal cancer: A systematic review. *Health Technol Assess*. 2019; 23(54): 1-102.
12. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med*. 2006; 166(10): 1092-1097.
13. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16(9): 606-613.
14. Svedlund J, Sjödin I, Dotevall G. GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988; 33(2): 129-134.
15. Kim S, Lee H, Park J. Anxiety and CEA levels in medical students with functional dyspepsia. *Psychonomic Med*. 2022; 84(5): 567-574.
16. Chen Y, Wang X, Li Z. Correlation between PHQ-9 scores and serum CA72-4 in young adults with depression. *J Affect Disord*. 2023; 320: 145-151.
17. Gronowitz E, Mellström D, Strandvik B. Serum CEA in healthy young adults: Relation to smoking and stress. *Ups J Med Sci*. 2001; 106(1): 31-38.
18. Li L, Zhang X, Liu Y, et al. Association of irritable bowel syndrome with serum CEA and CA19-9 in a large cohort of college students. *J Neurogastroenterol Motil*. 2024; 30(2): 210-218.
19. He Y, Song Y, Liao L, et al. Chronic stress induces upregulation of CEA via IL-6 in a mouse model of colorectal cancer. *Brain Behave Immun*. 2020; 87: 543-552.
20. Sun J, Wang X, Yang L, et al. Gut permeability and endotoxemia in medical students during examination stress. *J Psychonomic Res*. 2021; 147: 110526.
21. Yang GY, Zhang ZL, Liu C, et al. NF- κ B activation mediates the upregulation of CEACAM5 in colitis-associated cancer. *Inflamm Bowel Dis*. 2015; 21(8): 1813-1823.
22. Yu M, Lee S, Kim H. Mucin-1 (CA72-4) is induced by TNF- α in gastric epithelial cells. *Cytokine*. 2018; 110: 234-240.
23. Kim J, Park S, Lee D, et al. Prediction of serum CEA and CA72-4 using GAD-7, PHQ-9, and GSRS in medical students: A meta-regression approach. *J Psychonomic Res*. 2023; 165: 111128.
24. American Gastroenterological Association. Clinical Practice Update on the use of tumor markers in gastrointestinal cancers. *Gastroenterology*. 2021; 160(6): 2075-2085.
25. European Group on Tumor Markers (EGTM). Consensus guidelines for CA72-4. *Anticancer Res*. 2019; 39(11): 5847-5852.
26. Saito H, Kurose K, Nakao M, et al. Reference intervals for CEA and CA19-9 in healthy Japanese subjects. *Rinsho Byori*. 2017; 65(6): 621-626.
27. Peters SA, den Ruijter HM, Bots ML, et al. The role of inflammation in the association between stress and CEA: An animal study. *Psych neuroendocrinology*. 2019; 102: 123-131.
28. Reinisch W, Wang Y, Oddens BJ, et al. CEA reduction after anti-IL-6 therapy in Crohn's disease. *J Crohn's Colitis*. 2018; 12(1): 123-124.
29. Quek TT, Tam WW, Tran BX, et al. The global prevalence of anxiety among medical students: A meta-analysis. *Int J Environ Res Public Health*. 2019; 16(15): 2735.
30. Li X, Zhu Y, Zhang H, et al. Functional gastrointestinal disorders in Chinese medical students: Prevalence and risk factors. *J Dig Dis*. 2024; 25(1): 34-42.
31. Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer: European Group on Tumor Markers (EGTM) guidelines for clinical use. *Eur J Cancer*. 2003; 39(6): 718-727.