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Original Article

Risk factors and prediction model for cancer-related cognitive impairment in thyroid cancer patients

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Abstract: Background: Cognitive impairment is a common, yet often overlooked, complication in thyroid cancer patients, potentially influenced by various demographic, clinical, biochemical, and psychological factors. This study aims to analyze the prevalence and determinants of cancer-related cognitive impairment (CRCI) in thyroid cancer patients. Methods: A retrospective case-control study was conducted involving 246 thyroid cancer patients treated at our The First Affiliated Hospital of Soochow University from January 2021 to January 2023. Patients were categorized into high cognitive function (n = 125) and low cognitive function groups (n = 121) based on Mini Mental State Examination (MMSE) scores. Data were collected on demographic variables, Charlson Comorbidity Index (CCI), disease duration, clinical stage, blood test results, inflammatory factors (interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP)), psychological status (Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), Self-Esteem Scale (SES)), sleep quality (Pittsburgh Sleep Quality Index (PSQI)), and quality of life (36-item Short-Form Health Survey (SF-36)). Additionally, an external validation set was established, with patients being divided into a high cognitive level group (n = 135) and a low cognitive level group (n = 128), and the model's predictive performance was validated through the external dataset. Results: Factors significantly associated with lower cognitive function included age ($P < 0.001$), education level ($P < 0.001$), CCI scores ($P < 0.001$), disease duration ($P < 0.001$), clinical stage ($P = 0.003$), IL-6 ($P < 0.001$), IL-8 ($P = 0.005$), TNF-α ($P < 0.001$) and CRP ($P < 0.001$). SDS ($P < 0.001$), SAS ($P < 0.001$) and PSQI ($P < 0.001$) were also associated with reduced cognitive function. The Least Absolute Shrinkage and Selection Operator (LASSO) regression model demonstrated strong predictive performance with an area under the curve (AUC) of 0.903 in the training set and an AUC of 0.835 in the validation set. Conclusion: CRCI in thyroid cancer patients is multifactorial, with significant contributions from demographic, clinical, inflammatory, and psychological factors. The developed predictive model may serve as a valuable tool in clinical practice for identifying thyroid cancer patients at high risk of cognitive impairment.

Keywords: Thyroid cancer, cognitive impairment, inflammatory markers, psychological distress, predictive model, LASSO regression.

Introduction

Cancer-related cognitive impairment (CRCI), also referred to as "chemo-brain", is a well-recognized but poorly understood consequence of cancer and its treatment [1]. Increasingly, CRCI is acknowledged as a significant contributor to decreased quality of life among cancer survivors [2]. Thyroid cancer, while typically associated with favorable prognoses and long-term survival, is no exception when it comes to impacting cognitive function [3]. Previous studies have primarily focused on more aggressive cancers like breast or lung cancer with fewer efforts directed at understanding CRCI in thyroid cancer patients [4].

Thyroid cancer is the most common endocrine malignancy, characterized by various histological subtypes including papillary, follicular, medullary, and anaplastic [5]. The primary treatment modalities - surgery, radioactive iodine therapy, thyroid hormone therapy, external beam radiation therapy, and, less frequently, chemotherapy - carry their own risks for inducing cognitive deficits [6]. For instance, thyroid hormone withdrawal, often required for diagnostic and therapeutic procedures, can lead to

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hypothyroidism, a condition associated with cognitive dysfunction [7].

Despite the relatively high survival rates, cognitive complaints in thyroid cancer survivors are common but remain underreported and underresearched [8]. The potential mechanisms underlying CRCI involve a complex interplay of direct neurotoxic effects of cancer therapies, metabolic and hormonal disruptions, psychological stress, and chronic inflammation [9]. Additionally, other factors like age, comorbid conditions, and baseline cognitive reserve appear to contribute to the variability in cognitive outcomes [10].

Innovative cancer treatments, including targeted therapies and immunotherapies, have further highlighted the need for comprehensive evaluations of their long-term cognitive effects [11]. Limited research thus far suggests that systemic inflammation - marked by elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) - may play a crucial role in the pathophysiology of CRCI [12]. These cytokines can cross the blood-brain barrier and induce neuroinflammation, ultimately impacting cognitive function [13].

In parallel, psychosocial factors, such as depression, anxiety, and sleep disturbances, prevalent among cancer patients have been consistently linked to cognitive impairment [14]. Psychological distress can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels, which negatively affect brain structures involved in cognition, such as the hippocampus [15]. Sleep disturbances, on their part, impair cognitive processes crucial for memory consolidation and executive function.

While there is a considerable understanding of CRCI in more aggressive cancers, a critical gap exists regarding the identification and quantification of risk factors for CRCI in thyroid cancer patients. This study aims to fill this gap by investigating a comprehensive set of demographic, clinical, biochemical, and psychological variables to identify those most significantly associated with CRCI in a cohort of thyroid cancer patients. Additionally, we developed a predictive model to facilitate early identification of at-risk individuals, thereby enabling timely and targeted interventions.

Materials and methods

Case selection

This retrospective case-control study included 246 patients diagnosed with thyroid cancer who were treated at our The First Affiliated Hospital of Soochow University between January 2021 and January 2023. Data collection involved gathering demographic information and various other metrics from the patients' records, such as general information, hematological test results, scores from psychological status scales like Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS) and Self-Esteem Scale (SES), sleep quality assessed through the Pittsburgh Sleep Quality Index (PSQI) scale, and quality of life measured by the 36-item Short-Form Health Survey (SF-36) scale. As this study did not involve interventional human therapy, patients' informed consent was waived. The First Affiliated Hospital of Soochow University ethics committee approved the conduct of such research. Participants were included in the study if they were over 18 years old, had no history of mental illness, complied with various treatments and examinations, met the diagnostic criteria for thyroid cancer confirmed through pathological examination, and had a unilateral lesion. Individuals were excluded if they had immune system dysfunction, a history of lymph node surgery, significant lesions in the heart, liver, or kidneys, or any additional thyroid-related medical history.

Based on their Mini Mental State Examination (MMSE) scores after 1 month treatment, patients were categorized into two groups: 125 individuals in a high cognitive function group and 121 in a low cognitive function group. Additionally, an external validation set was established, with patients being divided into a high cognitive function group (n = 135) and a low cognitive function group (n = 128). The MMSE is a well-known cognitive screening instrument used to evaluate various cognitive domains, including orientation, memory, attention, computational skills, language, and visuospatial abilities. The exam consists of 30 points, with lower scores corresponding to higher levels of significant cognitive impair-

ment. The reliability of the MMSE is supported by a Cronbach's alpha coefficient of 0.78 [16]. A score of 22 or above indicates a high level of cognitive function, while scores below 22 signify a lower cognitive level.

Charlson comorbidity index (CCI)

The CCI is a frequently utilized system for evaluating a patient's one-year mortality risk due to comorbid conditions. This index considers 19 different chronic diseases, each assigned a weight between 1 and 6 points, reflecting the severity. Higher total scores represent a greater burden of comorbidities.

Treatment methods

The treatment approach for thyroid cancer was determined by the tumor's type, size, location, and lymph node involvement. The most prevalent approach involved excising part or all of the thyroid gland and performing a lymph node dissection in the neck. Remaining or metastatic cancer cells were treated with Radioiodine (I-131) therapy. Following thyroidectomy, patients were instructed to take lifelong thyroid hormone replacements (such as levothyroxine) to substitute the hormones that the thyroid gland would normally produce. External beam radiation therapy, targeted therapy, or chemotherapy were used to eradicate specific types of residual cancer cells or advanced-stage cancer.

Blood testing

Blood markers were detected 2 months after treatment. Specifically, 5 ml of fasting venous blood was collected from the patients before 8 am to perform the following tests. A DxH800 blood analyzer (Beckman Coulter, Inc., Brea, CA, USA) was used to assess red blood cells, white blood cells, neutrophils, lymphocytes, eosinophils, basophils, hemoglobin, and platelets. A BECKMAN Synchronlx20 fully automated biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA) was employed to measure CRP levels using the rate scattering turbidity method. Ethylenediaminetetraacetic acid was used to anticoagulate whole blood, and erythrocyte sedimentation rate (ESR) was measured with a TEST 1 fully automated erythrocyte sedimentation rate analyzer (ALIfax, Inc., Italy). The blood was centrifuged at 3000 rpm for 5 minutes, and the supernatant was collected to measure IL-6, IL-8, and TNF-α levels using enzyme-linked immunosorbent assay. During this process, the reagent kits included TNF-α (ab181421, Abcam, USA), IL-6 (ab178013, Abcam, USA), and IL-8 (ab185986, Abcam, USA).

Psychological and sleep assessment

The SDS scores range from 0 to 100, with higher scores indicating more severe negative emotions. The reliability of this scale is demonstrated by a Cronbach's alpha coefficient of 0.92 [17].

The SAS is a clinical tool to evaluate patients' subjective symptoms of anxiety. The cut-off score for the SAS is 50, with scores between 50 and 59 indicating mild anxiety, 60 to 69 indicating moderate anxiety, and 70 or above indicating severe anxiety. The scale has a Cronbach's alpha coefficient of 0.897 [18].

The SES is designed to evaluate an individual's overall sense of self-worth and self-acceptance. The total score is between 10 and 40 points. Higher scores indicate a higher level of self-esteem. According to reference data, scores below 25 suggest low self-esteem, scores between 26 and 32 indicate moderate self-esteem, and scores above 33 reflect high self-esteem. The SES has a Cronbach's alpha coefficient of 0.86 [19].

The PSQI is a useful tool for assessing sleep quality in individuals with sleep disorders, mental health conditions, and even in the general population. The total PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality. The reliability of the PSQI is supported by a Cronbach's alpha coefficient of 0.71 [20].

Health survey Short-Form 36 (SF-36)

The SF-36 Quality of Life Scale was utilized to assess various aspects of patients' quality of life during their treatment, including social functioning, self-management, mental health, and daily activities. Higher scores on the SF-36 indicate a better quality of life. This scale has demonstrated good reliability, with a Cronbach's alpha coefficient of 0.814 [21].

Statistical method

Using G*Power 3.1.9.7, under the "t tests" option for "Means: Difference between two

independent means (two groups)", post hoc analysis with setting of two tails, Effect size d = 0.5, α err prob = 0.05, the sample sizes of the two groups, the Power (1-β err prob) was calculated to be 0.974.

Data analysis was performed using SPSS 29.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as [n (%)]. When the sample size ≥ 40 and the theoretical frequency T ≥ 5, the basic chi-square test formula was applied; when the sample size ≥ 40 but the theoretical frequency 1 ≤ T < 5, the corrected chi-square test formula was used. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. For normally distributed continuous variables, the data are presented as Mean ± SD, and the t-test with adjusted variance was applied. Non-normally distributed continuous variables are presented as median (25th percentile, 75th percentile) and analyzed using the Wilcoxon rank-sum test. Statistical significance was set at a two-tailed P < 0.05. Spearman correlation analysis was used to investigate the correlations between cognitive levels and various indicators. Indicators showing significant differences in both differential analysis and correlation analysis were included as covariates in logistic regression analysis. The area under the receiver operating characteristic curve (AUC) was used to evaluate the diagnostic efficacy of each indicator for cognitive levels. Cross-validation and decision curve analysis (DCA) analysis were used to evaluate the predictive model. A gradient boosting machine (GBM) algorithm was used to construct a combined predictive model.

Results

Demographic and baseline characteristics of the study population

In this study, we examined the demographic and baseline characteristics associated with cognitive impairment in the patients (**Table 1**). Patients in the low cognitive level group were significantly older (67.93 ± 5.32 years) compared to those in the high cognitive level group (64.14 ± 7.56 years; P < 0.001). Educational attainment also showed a significant difference, with the high cognitive level group having more individuals with college education (53 vs. 22) and fewer individuals with primary school education (25 vs. 46) (P < 0.001). The CCI was higher in the low cognitive level group (2.57 ± 0.73) than in the high cognitive level group (2.11 ± 0.64; P < 0.001). Additionally, the average disease duration was longer in the low cognitive level group (12.61 ± 3.17 months) compared to the high cognitive level group (10.37 ± 3.02 months; P < 0.001). Clinical stage presented a significant association, with a higher percentage of patients in stage III/IV in the low cognitive level group compared to the high cognitive level group (P = 0.003). No significant differences were observed in body mass index (P = 0.592), gender distribution (P = 0.208), marital status (P = 0.257), smoking status (P = 0.095), drinking status (P = 0.088), hypertension (P = 0.198), diabetes mellitus (P = 0.132), or treatment methods (P = 0.894). These results suggest that age, education level, comorbidity burden, disease duration, and clinical stage are significant risk factors for cognitive impairment among thyroid cancer patients.

Routine blood test before treatment

The comparison of routine blood test results before treatment between the high cognitive level group and the low cognitive level group showed no statistically significant differences (**Table 2**). ESR was slightly higher in the high cognitive level group (35.83 ± 5.20 mm/h) compared to the low cognitive level group (34.76 ± 5.15 mm/h), but this difference did not reach statistical significance (P = 0.105). Similarly, red blood cell counts were higher in the high cognitive level group (5.44 ± 0.50 × 10^6/μL) than in the low cognitive level group (5.32 ± 0.52 × 10^6/μL; P = 0.067), although this was not statistically significant. White blood cell counts (P = 0.764), neutrophil counts (P = 0.966), lymphocyte counts (P = 0.832), eosinophil counts (P = 0.808), basophil counts (P = 0.290), hemoglobin levels (P = 0.973), and platelet counts (P = 0.990) were all comparable between the two groups with no significant differences observed. These results suggest that routine blood parameters before treatment do not significantly differ between thyroid cancer patients with high and low cognitive function levels.

Serum inflammatory factors

The comparison of serum inflammatory factors between thyroid cancer patients with high and

Table 1. Demographic and baseline characteristics of the study population

Parameters	High cognitive level group (n = 125)	Low cognitive level group (n = 121)	t/χ^2	*P* value
Age (years)	64.14 ± 7.56	67.93 ± 5.32	4.225	< 0.001
Body Mass Index (kg/m^2)	23.68 ± 3.24	23.43 ± 4.11	0.537	0.592
Gender (male/female)	40/85	29/92	1.588	0.208
Education Level			19.325	< 0.001
Primary School	25	46		
Secondary School	47	53		
College	53	22		
Married [n (%)]			1.284	0.257
Yes	90	78		
Smoking (yes/no)	35	47	2.783	0.095
Drinking (yes/no)	20	31	2.902	0.088
Hypertension [n (%)]			1.660	0.198
Yes	31	40		
Diabetes Mellitus [n (%)]			2.272	0.132
Yes	15	24		
CCI (Scores)	2.11 ± 0.64	2.57 ± 0.73	5.209	< 0.001
Average Disease Duration (Months)	10.37 ± 3.02	12.61 ± 3.17	5.669	< 0.001
Clinical Stage			8.542	0.003
I/II	81	55		
III/IV	44	46		
Treatment Method [n (%)]			None	0.894
Excision Surgery	77	73		
Radioiodine (I-131) Therapy	20	22		
Thyroid Hormone Replacement Therapy	11	14		
External Radiation Therapy	10	6		
Targeted Therapy	4	4		
Chemotherapy	3	2		

Note: CCI: Charlson Comorbidity Index.

Table 2. Comparison of routine blood test before treatment

Parameters	High cognitive level group (n = 125)	Low cognitive level group (n = 121)	t	*P* value
ESR (mm/h)	35.83 ± 5.20	34.76 ± 5.15	1.626	0.105
Red blood cell (1 × 10^6/μL)	5.44 ± 0.50	5.32 ± 0.52	1.838	0.067
White blood cell (1 × 10^3/μL)	7.38 ± 1.45	7.32 ± 1.48	0.301	0.764
Neutrophil (1 × 10^3/μL)	4.32 ± 0.98	4.33 ± 1.01	0.042	0.966
Lymphocyte (1 × 10^3/μL)	2.03 ± 0.62	2.05 ± 0.65	0.212	0.832
Eosinophil (1 × 10^2/μL)	0.28 ± 0.04	0.28 ± 0.03	0.244	0.808
Basophil (1 × 10/μL)	0.09 ± 0.03	0.09 ± 0.03	1.060	0.290
Hemoglobin (g/L)	149.4 ± 23.50	149.5 ± 23.90	0.033	0.973
Platelet (1 × 10^3/μL)	215.8 ± 118.5	215.6 ± 119.2	0.013	0.990

Note: ESR: erythrocyte sedimentation rate.

low cognitive levels revealed significant differences (**Figure 1**). The low cognitive level group exhibited higher levels of IL-6 (3.22 ± 1.02 ng/L) compared to the high cognitive level group (2.83 ± 0.81 ng/L; P < 0.001). Similarly, IL-8 levels were significantly elevated in the low

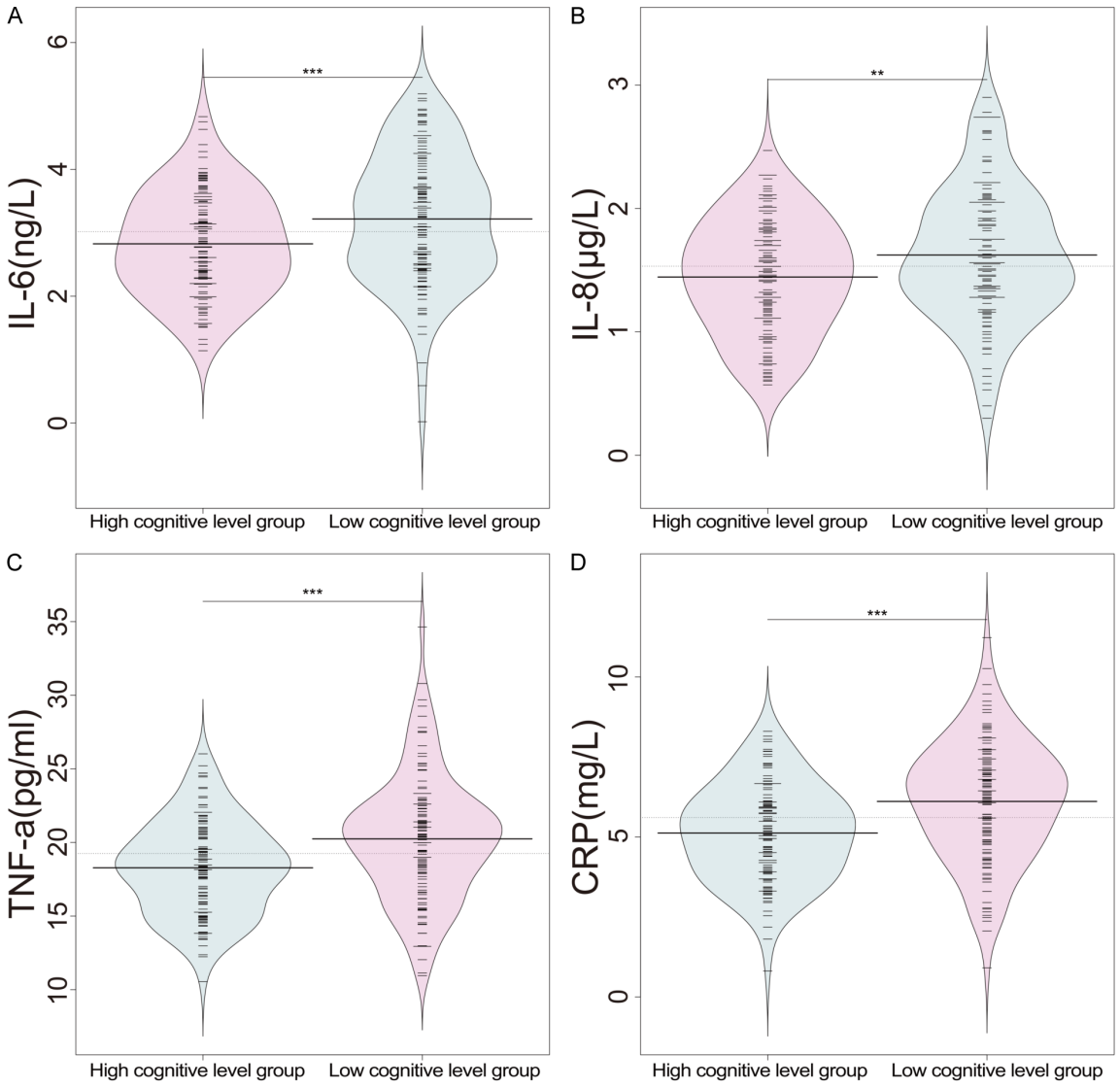

Figure 1. Comparison of serum inflammatory factors before treatment. A: IL-6 (ng/L); B: IL-8 (μg/L); C: TNF-α (pg/ml); D: CRP (mg/L). Note: IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein.

cognitive level group (1.62 ± 0.53 μg/L) versus the high cognitive level group (1.44 ± 0.45 μg/L; P = 0.005). TNF-α levels were also higher in the low cognitive level group (20.24 ± 4.22 pg/ml) compared to the high cognitive level group (18.28 ± 3.15 pg/ml; P < 0.001). Moreover, CRP levels were significantly increased in the low cognitive level group (6.11 ± 1.86 mg/L) compared to the high cognitive level group (5.12 ± 1.48 mg/L; P < 0.001). These results suggest that elevated serum inflammatory factors, including IL-6, IL-8, TNF-α, and CRP, are associated with lower cognitive levels in thyroid cancer patients.

Psychological and sleep status before treatment

The comparison of psychological and sleep status before treatment showed significant differences between the high and low cognitive level groups (**Figure 2**). The low cognitive level group had higher SDS scores (55.68 ± 7.01) compared to the high cognitive level group (52.13 ± 8.12; P < 0.001). Similarly, the SAS scores were significantly elevated in the low cognitive level group (59.42 ± 6.04) versus the high cognitive level group (56.54 ± 7.16; P < 0.001). The PSQI scores also indicated worse sleep quality in the

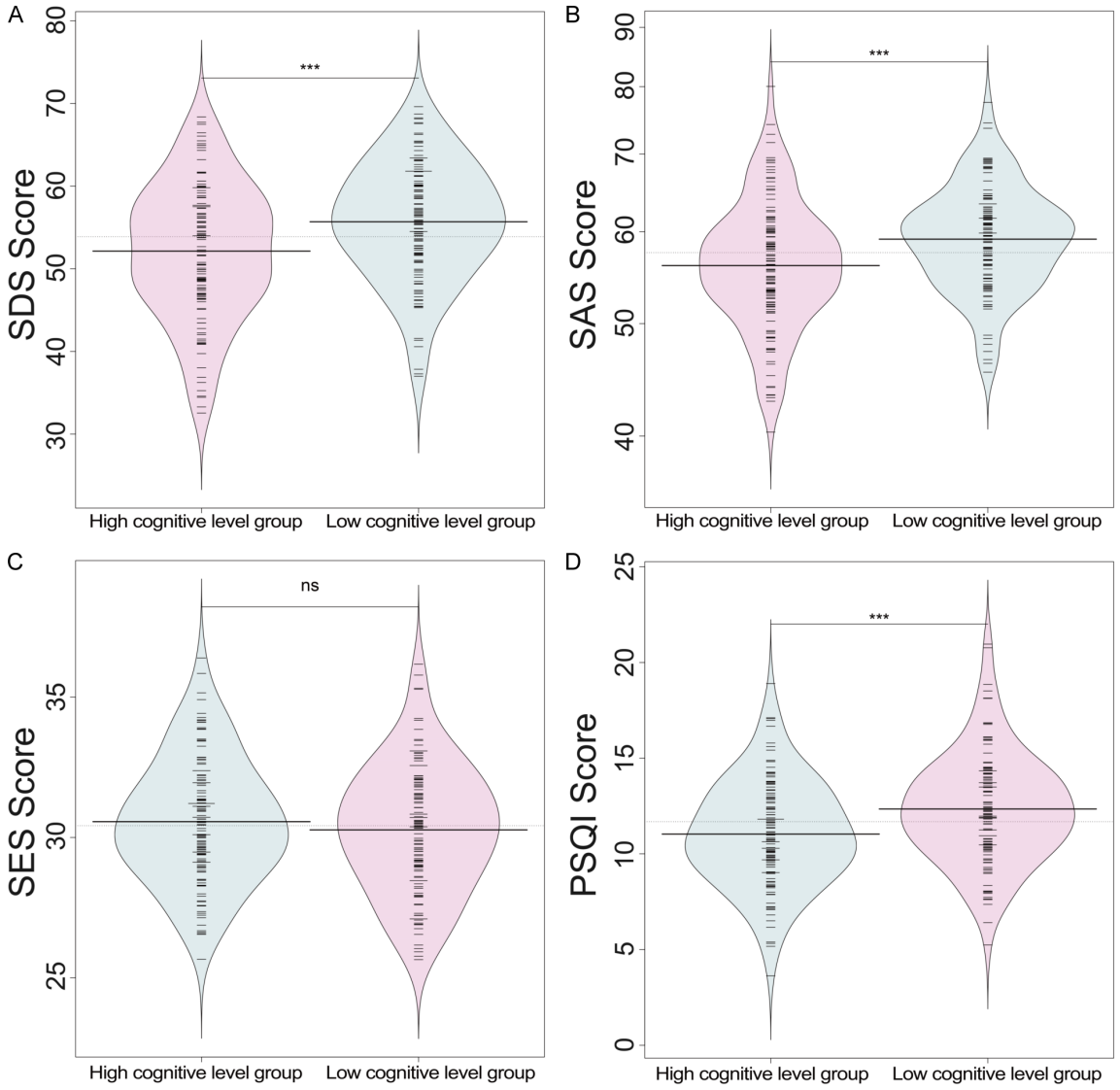

Figure 2. Comparison of psychological and sleep status before treatment. A: SDS Score; B: SAS Score; C: SES Score; D: PSQI Score. Note: SDS: Self Rating Depression Scale; SAS: Self-Rating Anxiety Scale; SES: Self Esteem Scale; PSQI: Pittsburgh sleep quality index.

low cognitive level group (12.35 ± 2.83) compared to the high cognitive level group (11.03 ± 2.75; P < 0.001). There was no significant difference in the SES scores between the two groups (P = 0.304). These findings suggest that higher levels of depression, anxiety, and poorer sleep quality are associated with lower cognitive function in thyroid cancer patients.

Quality of life before treatment (SF-36)

The comparison of quality of life before treatment between thyroid cancer patients with high and low cognitive levels demonstrated no statistically significant differences across the measured parameters (**Table 3**). Self-management scores were slightly higher in the high cognitive level group (57.28 ± 7.01) compared to the low cognitive level group (55.92 ± 7.12), but this difference was not significant (P = 0.132). Similarly, physiological function scores did not differ significantly between the high cognitive level group (49.06 ± 9.70) and the low cognitive level group (46.83 ± 9.43; P = 0.069). Social function scores were also comparable between the high cognitive level group (58.79 ± 7.01) and the low cognitive level group (57.92 ± 6.54; P = 0.315). Therefore, these results sug-

Table 3. Comparison of quality of life (SF-36) between two groups of patients before treatment

Parameters	High cognitive level group (n = 125)	Low cognitive level group (n = 121)	t	P
Self management	57.28 ± 7.01	55.92 ± 7.12	1.513	0.132
Physiological function	49.06 ± 9.70	46.83 ± 9.43	1.827	0.069
Social function	58.79 ± 7.01	57.92 ± 6.54	1.007	0.315

Table 4. Correlation analysis of factors influencing cancer-related cognitive impairment in thyroid cancer patients

	r	P
Age (years)	0.260	< 0.001
Education Level	-0.274	< 0.001
CCI (Scores)	0.317	< 0.001
Average Disease Duration (Months)	0.341	< 0.001
Clinical Stage	0.195	0.002
IL-6 (ng/L)	0.210	< 0.001
IL-8 (μg/L)	0.179	0.005
TNF-α (pg/ml)	0.256	< 0.001
CRP (mg/L)	0.283	< 0.001
SDS Score	0.228	< 0.001
SAS Score	0.213	< 0.001
PSQI Score	0.230	< 0.001

Note: CCI: Charlson Comorbidity Index; IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein; SDS: Self Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh sleep quality index.

gest that quality of life, as assessed by the SF-36, does not significantly differ between thyroid cancer patients with high and low cognitive levels before treatment.

Correlation analysis of factors influencing CRCI in thyroid cancer patients

The correlation analysis of factors influencing CRCI in thyroid cancer patients identified several significant associations (**Table 4**). Age (r = 0.260, P < 0.001), CCI scores (r = 0.317, P < 0.001), average disease duration in months (r = 0.341, P < 0.001), clinical stage (r = 0.195, P = 0.002), IL-6 levels (r = 0.210, P < 0.001), IL-8 levels (r = 0.179, P = 0.005), TNF-α levels (r = 0.256, P < 0.001), and CRP levels (r = 0.283, P < 0.001) were all positively correlated with cognitive impairment. Psychological and sleep status parameters including SDS scores (r = 0.228, P < 0.001), SAS scores (r = 0.213, P < 0.001), and PSQI scores (r = 0.230, P < 0.001) also showed significant positive correlations with cognitive impairment. Conversely, higher education level was negatively correlated with cognitive impairment (r = -0.274, P < 0.001). These findings underscore the multifactorial nature of CRCI, involving demographic, clinical, biochemical, and psychological factors.

Multivariate logistic regression analysis of factors affecting CRCI in thyroid cancer patients

Multivariate logistic regression analysis identified several significant predictors of CRCI in thyroid cancer patients (**Table 5**). Increasing age (OR, 1.160; 95% CI, 1.087-1.237; P < 0.001) and advanced clinical stage (OR, 1.335; 95% CI, 1.150-1.751; P = 0.008) were associated with higher odds of cognitive impairment. Higher education level was a protective factor (OR, 0.340; 95% CI, 0.194-0.596; P < 0.001). Higher CCI scores significantly increased the odds of cognitive impairment (OR, 3.486; 95% CI, 1.876-6.477; P < 0.001). Longer average disease duration was also a significant risk factor (OR, 1.395; 95% CI, 1.205-1.617; P < 0.001). Elevated levels of serum inflammatory factors, including IL-6 (OR, 1.878; 95% CI, 1.202-2.933; P = 0.006), IL-8 (OR, 4.150; 95% CI, 1.713-10.054; P = 0.002), TNF-α (OR, 1.176; 95% CI, 1.043-1.325; P = 0.008), and CRP (OR, 1.597; 95% CI, 1.244-2.049; P < 0.001) were also significant predictors. Psychological distress, indicated by higher SDS scores (OR, 1.072; 95% CI, 1.017-1.130; P = 0.010) and SAS scores (OR, 1.122; 95% CI, 1.054-1.195; P < 0.001), along with poorer sleep quality, as measured by PSQI scores (OR, 1.252; 95% CI, 1.087-1.440; P = 0.002), were also significantly associated with cognitive impairment. These findings highlight the multifactorial etiology of cognitive impairment in this patient population and underscore the importance of addressing both clinical and psychosocial factors in predicting and managing this condition.

Establishment of prediction model

After our analysis to identify risk factors, we developed a predictive model for CRCI in patients diagnosed with thyroid cancer by employing the Least Absolute Shrinkage and

Table 5. Multivariate logistic regression analysis of factors affecting cancer-related cognitive impairment in thyroid cancer patients

	Coefficient	Std. Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Age (years)	0.148	0.033	4.465	< 0.001	1.160	1.087	1.237
Education Level	-1.078	0.286	-3.771	< 0.001	0.340	0.194	0.596
CCI (Scores)	1.249	0.316	3.951	< 0.001	3.486	1.876	6.477
Average Disease Duration (Months)	0.333	0.075	4.441	< 0.001	1.395	1.205	1.617
Clinical Stage	1.093	0.411	-2.656	0.008	1.335	1.150	1.751
IL-6 (ng/L)	0.630	0.228	2.769	0.006	1.878	1.202	2.933
IL-8 (μg/L)	1.423	0.451	3.152	0.002	4.150	1.713	10.054
TNF-α (pg/ml)	0.162	0.061	2.652	0.008	1.176	1.043	1.325
CRP (mg/L)	0.468	0.127	3.677	< 0.001	1.597	1.244	2.049
SDS Score	0.069	0.027	2.570	0.010	1.072	1.017	1.130
SAS Score	0.115	0.032	3.584	< 0.001	1.122	1.054	1.195
PSQI Score	0.224	0.072	3.129	0.002	1.252	1.087	1.440

Note: CCI: Charlson Comorbidity Index; IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein; SDS: Self Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh sleep quality index.

Selection Operator (LASSO) regression technique (**Figure 3**). This method facilitated the selection of variables most strongly associated with CRCI by penalizing coefficients of less relevant predictors toward zero. The coefficient paths generated as a function of the L1 norm and log lambda demonstrated the stability of selected variables across different penalty levels. Specifically, 12 independent influencing factors (age, education level, CCI scores, average disease duration, clinical stage, IL-6, IL-8, TNF-α, CRP, SDS score, SAS score, and PSQI score) were consistently retained in the model as lambda increased, indicating their robust association with the outcome. During model training, this study employed ten-fold cross-validation ten times to avoid overfitting risks. In each cross-validation iteration, the dataset was first divided into ten parts, with nine parts used to train the model and obtain the optimal parameters. Finally, the model's predictive performance was evaluated on the remaining one part of the data. The predictive performance of the model was evaluated using AUC, which yielded an impressive value of 0.903. This suggests high discriminatory power in distinguishing between thyroid cancer patients who will develop CRCI from those who will not.

Demographic and baseline characteristics of the verification set

A total of 263 patients were selected for external validation, including 135 patients with high cognitive levels and 128 patients with low cognitive levels. Among them, patients in the low cognitive level group had significantly higher age (67.47 ± 6.28 vs. 65.24 ± 7.38, t = 2.637, P = 0.009), CCI score (2.64 ± 0.53 vs. 2.48 ± 0.56, t = 2.410, P = 0.017), and disease duration (11.48 ± 2.65 vs. 10.49 ± 2.16, t = 3.313, P = 0.001) compared to patients in the high cognitive level group (**Table 6**). Patients in the high cognitive level group demonstrated significantly higher education levels (χ^2 = 25.032, P < 0.001) and lower clinical stages (χ^2 = 8.251, P = 0.004). However, there were no significant differences between the two groups in other demographic and baseline characteristics (P > 0.05). This was consistent with the data from the training set, indicating that age, education level, CCI score, disease duration, and clinical stage significantly influenced patients' cognitive levels.

Prediction indicators (validation set)

As shown in **Table 7**, the two groups in the validation set also exhibited significant differences in predictive indicators. Patients in the low cognitive level group showed significantly elevated levels of IL-6 (P = 0.001), IL-8 (P = 0.003), TNF-α (P = 0.002), CRP (P = 0.024), SDS scores (P = 0.026), SAS scores (P = 0.003), and PSQI scores (P = 0.011). This suggests that IL-6, IL-8, TNF-α, CRP, SDS score, SAS score, and PSQI score significantly influence patients' cognitive levels.

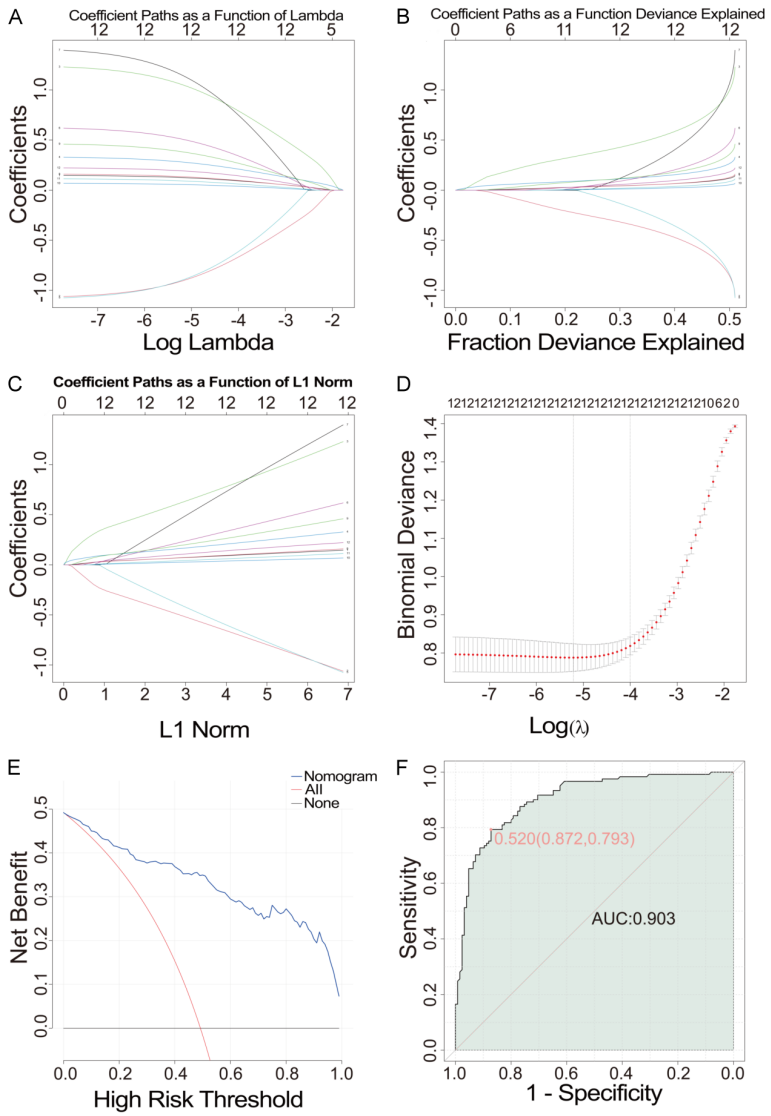

Figure 3. Establishment of prediction model. A: Coefficient paths as a function of lambda; B: Coefficient paths as a function deviance explained; C: Coefficient paths as a function of L1 norm; D: Cross validation; E: DCA plot; F: ROC model evaluated the predictive performance of indicators related to cognitive impairment in thyroid cancer. Note: DCA: decision curve analysis; ROC: receiver operating characteristic.

ROC (validation set)

Combining all predictive indicators (age, education level, CCI scores, average disease duration, clinical stage, IL-6, IL-8, TNF-α, CRP, SDS score, SAS score, and PSQI score), the model demonstrated high predictive performance with an AUC of 0.835 in the validation set (**Figure 4**). This suggests that the combined indicators have good predictive efficacy for predicting CRCI in thyroid cancer patients.

Discussion

The present study thoroughly investigated the risk factors associated with CRCI in thyroid cancer patients and subsequently established a predictive model to facilitate the identification of at-risk individuals. A wide array of variables, including demographic, clinical, biochemical, and psychological parameters, were meticulously examined to delineate their impact on cognitive function. The notable findings highlight the intricate interplay of these factors, offering important implications for clinical practice and future research.

The study revealed that increasing age was a significant risk factor for CRCI in thyroid cancer patients. This observation aligns with the general understanding of cognitive aging [22], where neurobiological changes, such as reduced neurogenesis, synaptic plasticity decline, and increased vulnerability to neurodegenerative processes, collectively contribute to cognitive decline. Aging is also accompanied by a higher cumulative burden of comorbidities, which can exacerbate cognitive impairment through multiple pathways, including chronic inflammation, vascular pathology, and metabolic disturbances [23]. Previous literature has also reported that increasing age is closely associated with cognitive decline, and cancer patients in older populations are more likely to be affected by cognitive impairments [24]. Educational attainment emerged as a protective factor against CRCI, underscoring the 'cognitive reserve' hypothesis. Higher education levels are associated with enhanced neural efficiency, greater synaptic density, and more robust neural networks, which confer resilience

Table 6. Demographic and baseline characteristics of the verification set

Parameters	High cognitive level group (n = 135)	Low cognitive level group (n = 128)	t/χ^2	*P* value
Age (years)	65.24 ± 7.38	67.47 ± 6.28	2.637	0.009
Body Mass Index (kg/m^2)	23.15 ± 2.16	23.38 ± 2.47	0.801	0.424
Gender (male/female)	52 (38.52%)/83 (61.48%)	42 (32.81%)/86 (67.19%)	0.931	0.334
Education Level			25.032	< 0.001
Primary School	25 (18.52%)	38 (29.69%)		
Secondary School	44 (32.59%)	65 (50.78%)		
College	66 (48.89%)	25 (19.53%)		
Married [n (%)]			2.665	0.103
Yes	115 (85.19%)	99 (77.34%)		
Smoking (yes/no)	41 (30.37%)/94 (69.63%)	45 (35.16%)/83 (64.84%)	0.684	0.408
Drinking (yes/no)	28 (20.74%)/107 (79.26%)	32 (25.00%)/96 (75.00%)	0.677	0.411
Hypertension [n (%)]			0.684	0.408
Yes	41 (30.37%)	45 (35.16%)		
Diabetes Mellitus [n (%)]			0.219	0.640
Yes	24 (17.78%)	20 (15.62%)		
CCI (Scores)	2.48 ± 0.56	2.64 ± 0.53	2.410	0.017
Average Disease Duration (Months)	10.49 ± 2.16	11.48 ± 2.65	3.313	0.001
Clinical Stage			8.251	0.004
I/II	93 (68.89%)	66 (51.56%)		
III/IV	42 (31.11%)	62 (48.44%)		
Treatment Method [n (%)]			1.502	0.913
Excision Surgery	78 (57.78%)	72 (56.25%)		
Radioiodine (I-131) Therapy	21 (15.56%)	25 (19.53%)		
Thyroid Hormone Replacement Therapy	16 (11.85%)	14 (10.94%)		
External Radiation Therapy	10 (7.41%)	8 (6.25%)		
Targeted Therapy	6 (4.44%)	7 (5.47%)		
Chemotherapy	4 (2.96%)	2 (1.56%)		

Note: CCI: Charlson Comorbidity Index.

Table 7. Prediction indicators (validation set)

Parameters	High cognitive level group (n = 135)	Low cognitive level group (n = 128)	t	*P* value
IL-6 (ng/L)	2.94 ± 0.64	3.28 ± 0.98	3.314	0.001
IL-8 (μg/L)	1.41 ± 0.36	1.59 ± 0.62	2.955	0.003
TNF-α (pg/ml)	19.16 ± 3.52	20.64 ± 4.15	3.134	0.002
CRP (mg/L)	5.84 ± 1.38	6.29 ± 1.75	2.272	0.024
SDS score	54.48 ± 6.15	56.24 ± 6.57	2.244	0.026
SAS score	56.47 ± 6.23	58.75 ± 6.18	2.984	0.003
PSQI score	11.75 ± 2.15	12.41 ± 2.06	2.559	0.011

Note: IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein; SDS: Self Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh sleep quality index.

against pathological insults [25]. Cognitive reserve can delay the onset of clinical manifestations of cognitive impairment, as individuals with higher reserve can utilize alternative neural pathways to compensate for brain damage caused by various factors, including cancer and its treatment [26]. Previous studies have shown that individuals with higher education levels exhibit stronger adaptability and resilience when facing cognitive challenges [27].

The CCI was significantly correlated with cognitive impairment, which is consistent with previous studies highlighting the impact of multimor-

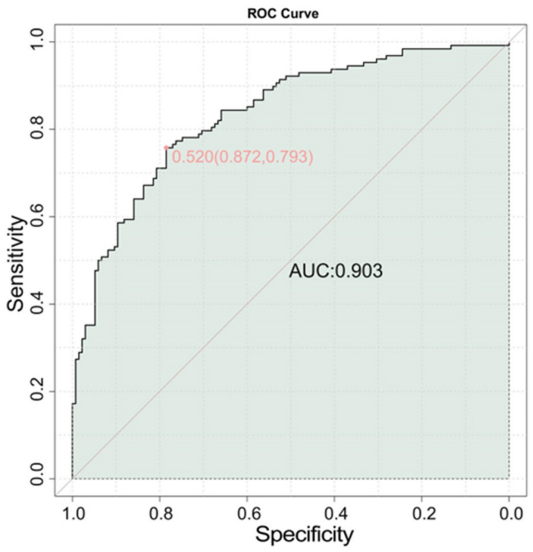

Figure 4. ROC model evaluated the predictive performance of indicators related to cognitive impairment in thyroid cancer (validation set). Note: ROC: receiver operating characteristic.

bidity on cognitive health [28]. Comorbid conditions, such as cardiovascular diseases, diabetes, and chronic inflammatory states, can adversely affect cognitive function through mechanisms like reduced cerebral perfusion, oxidative stress, and the pro-inflammatory milieu [29]. The additive burden of multiple chronic diseases can synergistically impair cognitive processes, exacerbating cognitive decline in cancer patients [30]. Longer disease duration was another significant risk factor for CRCI. Prolonged exposure to cancer-related physiological and psychological stressors can have a cumulative detrimental effect on cognitive function. Chronic stress, persistent inflammation, and the metabolic demands of sustained cancer progression can disrupt neural homeostasis and promote cognitive decline [31]. Furthermore, longer disease duration often implies extended periods of cancer treatment, which can have neurotoxic effects contributing to cognitive impairment. The clinical stage of cancer was associated with cognitive impairment, suggesting that patients with more advanced disease stages exhibit greater susceptibility to CRCI. Several factors could contribute to this phenomenon: First, advanced-stage cancer typically correlates with a higher tumor burden, which could directly or indirectly affect brain function. Tumor-related factors like metabolic changes, hormonal imbalances, and systemic inflammation may detrimentally impact cognitive processes [32]. Additionally, patients with advanced-stage cancer are often under significant psychological stress due to poorer prognoses and more intense treatment regimens. Elevated psychological distress, including anxiety and depression, is known to adversely affect cognitive function [33].

Elevated levels of serum inflammatory factors, such as IL-6, IL-8, TNF-α, and CRP, were strongly associated with lower cognitive levels. Chronic inflammation is a well-established contributor to cognitive decline, with inflammatory cytokines exerting neurotoxic effects, disrupting blood-brain barrier integrity, and impairing neurogenesis and synaptic plasticity [34]. Cancer-related systemic inflammation can exacerbate these processes, driving cognitive impairment. The findings underscore the role of the neuroinflammatory model of cognitive decline, advocating for the importance of managing systemic inflammation in cancer patients to preserve cognitive function.

Psychological distress, indicated by higher SDS and SAS scores, along with poorer sleep quality, as measured by PSQI scores, were also significant predictors of CRCI. Depression and anxiety are common comorbidities in cancer patients and have well-documented adverse effects on cognitive function. These psychological conditions can contribute to cognitive impairment through various mechanisms, including dysregulation of the HPA axis, increased systemic inflammation, and direct neurotoxic effects of stress hormones [35]. Poor sleep quality further exacerbates cognitive decline by impairing processes such as memory consolidation, synaptic plasticity, and neuronal repair, which are crucial for maintaining cognitive function. These findings highlight the importance of comprehensive psychosocial care in cancer management to address these modifiable risk factors.

The multivariate logistic regression analysis offered a robust predictive model for CRCI, with significant variables including age, education level, CCI scores, disease duration, clinical stage, serum inflammatory markers (IL-6, IL-8, TNF-α, and CRP), SDS scores, SAS scores, and PSQI scores. The high discriminatory power of the model, as indicated by the AUC, underscores its clinical utility in early identification of

patients at high risk for CRCI. This predictive capability is crucial for implementing personalized interventions, optimizing treatment protocols, and providing targeted psychosocial support to mitigate cognitive decline.

The findings of this study hold significant implications for clinical practice. First, routine cognitive screening should be considered for thyroid cancer patients, especially those with identified risk factors such as advanced age, lower education levels, high comorbidity burden, and longer disease duration. Early detection of cognitive impairment allows for timely interventions aimed at preserving cognitive function. Second, managing systemic inflammation through appropriate therapeutic strategies could be a key component of supportive care in cancer patients. Anti-inflammatory agents, lifestyle modifications, and dietary interventions targeting inflammation could potentially mitigate CRCI. Third, comprehensive psychosocial care addressing depression, anxiety, and sleep disturbances should be integrated into cancer care pathways. Psychotherapy, pharmacological treatments, and behavioral interventions could effectively alleviate psychological distress and improve sleep quality, thereby supporting cognitive health.

While this study provides valuable insights into the risk factors and predictive modeling of CRCI in thyroid cancer patients, several limitations must be acknowledged. Firstly, the retrospective design limits the ability to establish causal relationships and may introduce selection bias. Secondly, the study cohort was derived from a single institution, potentially affecting the generalizability of the findings to broader populations. Thirdly, cognitive function was assessed using the MMSE, which, while widely used, may not capture subtle cognitive impairments that could be detected with more comprehensive neuropsychological testing. Additionally, the variations in treatment plans and combination therapies within the study cohort may introduce bias in the results. Lastly, the reliance on self-reported psychological and sleep quality measures could introduce response bias. Future studies with longitudinal designs, multicenter cohorts, and more detailed cognitive assessments are warranted to build upon these findings and further elucidate the mechanisms underlying CRCI in thyroid cancer patients. Future research should delve deeper into the biological mechanisms linking cancer, its treatment, and cognitive impairment. Longitudinal studies examining the trajectory of cognitive changes over time and their association with inflammatory markers, stress hormones, and neuroimaging findings would offer valuable insights. Investigating the potential neuroprotective effects of different cancer treatment modalities, including targeted therapies and immunotherapies, could uncover new avenues for mitigating CRCI. Additionally, exploring the role of genetic and epigenetic factors in modulating susceptibility to CRCI could contribute to the development of personalized medicine approaches in oncology.

Conclusion

In conclusion, this study provides a comprehensive analysis of the multifactorial nature of CRCI in thyroid cancer patients. The identified risk factors, including age, education level, comorbidities, disease duration, clinical stage, serum inflammatory markers, psychological distress, and sleep quality, collectively contribute to the development of cognitive impairment. The predictive model established in this study offers a valuable tool for early identification and targeted intervention, ultimately aiming to enhance the quality of life in thyroid cancer patients.

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Disclosure of conflict of interest

None.

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