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ORIGINAL RESEARCH

Routine Blood Tests as Predictive Tools for Differentiating Follicular Thyroid Carcinoma From Follicular Adenoma

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Background: Thyroid cancer is the most common endocrine malignancy, with an increasing incidence rate, particularly among adolescents. Follicular thyroid carcinoma (FTC), though less common than papillary thyroid carcinoma (PTC), presents greater diagnostic challenges, especially when differentiating from follicular adenoma (FA). Current diagnostic methods lack specificity, underscoring the need for a simple, cost-effective predictive model for FTC.This study aimed to develop a predictive scoring system based on routine blood biomarkers to distinguish between FTC and FA, facilitating early diagnosis and treatment.

Methods: A retrospective, single-center case-control study was conducted on patients diagnosed with FTC and FA at Renmin Hospital of Wuhan University from 2016 to 2022. Patients' demographic, clinicopathological characteristics, and preoperative blood biomarker data were analyzed. Statistical tests, including chi-square, t-tests, and Mann–Whitney *U*-tests, were used to compare biomarkers. Significant variables were included in univariate and multivariate logistic regression analyses, leading to the development of a scoring system. The model's performance was assessed using receiver operating characteristic (ROC) curves.

Results: The study included 23 patients with FA and 26 patients with FTC. Seven blood biomarkers showed significant differences between the groups: ALB, DBIL, TBIL, LYM#, MCHC, RDW-SD, and WBC. Multivariate logistic regression identified ALB and WBC as key predictors, forming a scoring model (Score = 0.54 × ALB - 1.10 × WBC). The model exhibited strong predictive performance (AUC = 0.839), with sensitivity and specificity of 0.808 and 0.826, respectively.

Conclusion: The study developed a novel predictive model using routine blood biomarkers, offering a non-invasive, cost-effective tool for differentiating between FTC and FA. The model has significant clinical potential, providing a feasible alternative to conventional diagnostic techniques. Further multicenter studies and mechanistic investigations are warranted to validate and refine the model, enhancing its utility in clinical practice.

Keywords: follicular thyroid carcinoma, blood biomarkers, predictive model, albumin, early diagnosis

Introduction

The thyroid gland, consisting of two connected lobes, is one of the largest endocrine glands in the human body, weighing 20–30 g in adults. Thyroid lesions are often found on the gland, with a prevalence of 4%–7%. Most of them are asymptomatic, and thyroid hormone secretion is normal.[1] Thyroid cancer is the most prevalent endocrine malignancy, with its incidence rate doubling since the mid-1990s. Specifically, the incidence of thyroid cancer among adolescents has been increasing at an alarming rate, with an annual growth of over 4%.[2–5] Follicular thyroid carcinoma (FTC) is the second most prevalent thyroid malignancy, following papillary thyroid carcinoma (PTC), yet exhibits a markedly inferior survival rate compared to PTC.[6] Follicular adenoma (FA) and FTC are both neoplasms derived from follicular cells and characterized by microfollicular structures lined by cuboidal epithelial cells.[7] As a malignancy with a poorer prognosis, FTC is difficult to distinguish from FA using simple methods. This diagnostic challenge has hindered the early

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diagnosis and treatment of FTC, ultimately affecting the outcomes and prognosis of some patients. Therefore, developing a predictive model for the early screening and diagnosis of FTC has become a pressing need in clinical practice.

Prior studies on predicting FTC have predominantly concentrated on genetic mutations, including those in *TP53, FLT3, RAS*, and *PAX8/PPARγ* rearrangements.[8–10] Furthermore, some studies have described FTC based on clinico-pathological features and imaging characteristics, including nodule size, hypo echogenicity, lobulated or irregular margins, thick halo, microcalcifications, restricted diffusion, and cystic changes. However, these methods generally exhibit low specificity, limiting their clinical applicability.[11–14]

Blood laboratory tests conducted upon hospital admission are frequently utilized to facilitate the preparation of patients for impending medical interventions. A substantial body of evidence from numerous studies indicates that laboratory tests play an increasingly pivotal role in diagnosing and differentiating benign and malignant tumors.[15–17] Certain markers of inflammation based on circulating blood cells can serve as simple and convenient measures of systemic inflammatory responses and act as independent predictors, including for aggressive thyroid tumors.[18–20] Additionally, bilirubin (BIL) and lipoprotein levels in the comprehensive metabolic panel (CMP) have also been shown to be associated with various cancers.[21–23]

The objective of this study is to examine alterations in blood biomarkers between patients with FTC and those with FA through the utilization of routine blood tests. The aim is to devise a straightforward, cost-effective predictive scoring system to differentiate between FTC and FA, thereby enhancing the detection rate of FTC and facilitating early detection, diagnosis, and treatment.

Materials and Methods

Study Design and Patient Selection

This retrospective, single-center, case-control study was conducted at Renmin Hospital of Wuhan University, China. It was designed using the STROBE checklist for case-control studies (4th edition) (Supplementary Data 1).[24] The study design was reviewed and approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University (No. WDRY2024-K038), and retrospective data were handled with confidentiality. The study was conducted in compliance with the Declaration of Helsinki.

This study retrospectively reviewed the medical records of patients diagnosed with thyroid tumors who were treated at Renmin Hospital of Wuhan University from January 1, 2016, to December 31, 2022. Patient information, including medical history, physical examinations, laboratory blood tests, cytopathological results, histopathological findings, and imaging data (primarily ultrasound), was collected and reviewed by two researchers (JX. Wang & JW Wang). Patients were included for further data extraction and analysis if they met the following criteria: a) underwent total or partial thyroidectomy at our medical center, and b) histologically confirmed to have either FA or FTC after surgery. The exclusion criteria were as follows: a) age < 18 years, b) pregnancy or diagnosis of other malignancies, c) FA patients with thyroid malignancy, d) FTC patients with other thyroid malignancies, such as PTC, medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma (ATC), and e) incomplete medical records. A total of 23 patients with FA and 26 patients with FTC who met the inclusion criteria and did not meet any exclusion criteria were included in the FA and FTC groups, respectively.

Data Collection

The hospital information system documented patients' demographic and clinicopathological characteristics, including age, gender, history of hyperthyroidism, smoking history, alcohol consumption history, family history of malignancy, histological type and subtype, tumor size, cervical lymph node metastasis, extrathyroidal extension, and distant metastasis. TNM staging was performed by the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Blood samples (5 to 10 mL) were collected in the early morning before surgery and analyzed immediately for blood biomarkers using automated analyzers (ADVIA 2400: Siemens, Germany, and Sysmex XN-20 system: Kobe, Japan). The laboratory information system (LIS) was utilized to retrieve the results of the blood test, including blood cell counts, coagulation functions, thyroid function, liver function, and other pertinent data.

Statistical Analysis

Blood biomarkers with a frequency of less than 0.75 in the total patient sample were excluded from the statistical analysis. If the data exceeded the detection range, they were calculated as the upper or lower limit of detection. Categorical and ordinal data were expressed as numbers and percentages, while continuous data were presented as either the mean (standard deviation, SD) or the median. The Pearson chi-square test was employed for the analysis of categorical data. To ascertain whether continuous data exhibited homogeneity of variance and Gaussian distribution, respectively, Levene's test and the Shapiro–Wilk test were applied. Data that satisfied both the homogeneity of variance and Gaussian distribution criteria were analyzed using the *t*-test. Conversely, the Mann–Whitney *U*-test was employed to assess ordinal and continuous data that did not adhere to a Gaussian distribution. The results of the comparison of blood biomarkers were normalized using min-max normalization and visualized as a heatmap generated with SangerBox (V3.0).[25] Average linkage clustering with Pearson correlation distance was applied. All tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Subsequent binary univariate logistic regression analysis was conducted on blood biomarkers that demonstrated statistically significant differences. Variables with a p-value less than or equal to 0.05 were incorporated into the multivariate regression analysis. The scoring system formula was constructed by multiplying the variable values by their corresponding regression coefficients and summing the results. The predictive efficacy of the blood biomarkers and the scoring system in identifying RAIR was evaluated using receiver operating characteristic (ROC) curves. The Youden index, sensitivity, and specificity were then calculated based on the cutoff values. The statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Armonk, NY).

Results

Patient Demographics and Clinicopathological Characteristics

From January 1, 2016, to December 31, 2022, a total of 12,691 patients were diagnosed with thyroid tumors at our medical center. Among them, 808 patients had a pathological diagnosis of "follicular adenoma", and 50 patients were diagnosed with "follicular thyroid carcinoma" (Figure 1). A total of 97% (785) of the FA patients were excluded for various reasons, including the presence of FA with thyroid malignancies and incomplete medical records. Additionally, 48% (24) of the FTC patients were excluded due to conditions such as FTC with other thyroid carcinoma, diagnosis based solely on fine needle aspiration, and incomplete medical records. Ultimately, this study included 23 patients with a pathological diagnosis of only "follicular adenoma" in the FA group and 26 patients with a pathological diagnosis of only "follicular thyroid carcinoma" in the FTC group.

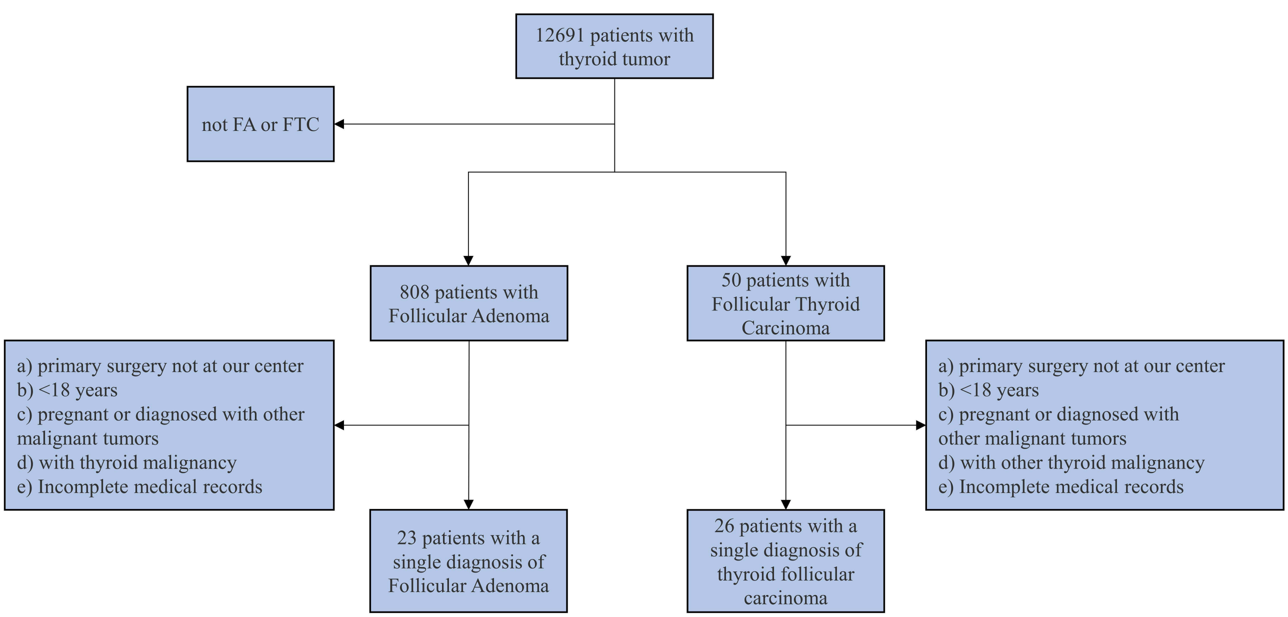

Figure 1 The flow chart of patient selection.

Table 1 Demographical and Clinicopathological Characteristics of Included Patients

Parameter	Total	FA	FTC	p.value
Number of patients	49	23	26	
Age	48.86 (16.01)	45.04 (15.09)	52.23 (16.32)	0.118
Age (≥55y, %)	20 (40.8)	7 (30.4)	13 (50.0)	0.245
Sex (female, %)	31 (63.3)	16 (69.6)	15 (57.7)	0.554
Tumor size (cm, SD)	3.278 (1.654)	3.034 (1.329)	3.488 (1.897)	0.348
Hyperthyroidism (%)	3 (6.1)	2 (8.7)	1 (3.8)	0.594
Alcohol consumption (%)	2 (4.1)	1 (4.3)	1 (3.8)	1
Smoking (%)	8 (16.3)	2 (8.7)	6 (23.1)	0.254
Family history of thyroid cancer (%)	1 (2.0)	1 (4.3)	0 (0)	0.469
Family history of other cancer (%)	6 (12.2)	5 (21.7)	1 (3.8)	0.086
Extrathyroidal extension (%)	19		19 (73.1)	
TNM (%)				
T1-3	21		21 (80.8)	
T4	5		5 (19.2)	
N0	9		9 (34.6)	
N1	17		17 (65.4)	
M0	23		23 (88.5)	
M1	3		3 (11.5)	

Abbreviation: SD, standard deviation.

We compared the demographic and clinicopathological characteristics of the FA and FTC groups (Table 1). The mean age was 48.86 years, with 40.8% of patients aged over 55 years, and 63.3% of the individuals were female. There was no statistically significant difference in tumor size between the groups (p = 0.348). Given that comorbidities, smoking, and alcohol consumption are known to affect circulating biomarkers, we assessed the differences between the two groups in these aspects.[26] There were no significant differences in hyperthyroidism (p = 0.594), alcohol consumption (p = 1), or smoking (p = 0.254). Since a family history of malignancy can influence an individual's risk of developing cancer, we separately analyzed the family history of thyroid cancer and other malignancies. There were no significant differences in family history of thyroid cancer (p = 0.469) or family history of other cancers (p = 0.086).

Given that benign tumors do not involve extrathyroidal extension or TNM staging, a separate statistical analysis was conducted for the FTC group. Among the patients with FTC, 73.1% (19 cases) exhibited extrathyroidal extension. Following the TNM staging system established by the American Joint Committee on Cancer (AJCC), 80.8% (21 cases) were classified as T1-3, while 19.2% (5 cases) were classified as T4. Furthermore, 34.6% (9 cases) were classified as N0, while 65.4% (17 cases) were N1. About distant metastasis, 88.5% (23 cases) were classified as M0, while 11.5% (3 cases) were designated as M1.

Comparison of Blood Biomarkers Between Groups

A preliminary evaluation of the data set included 317 blood biomarkers (all preoperative), and 75 items with a frequency greater than 75% were retained and processed for subsequent analysis (Supplementary Table 1 and Figure 1). Chi-square tests were employed for binary variables, t-tests were utilized for continuous variables that exhibited a Gaussian distribution and homogeneity of variance, and the Mann–Whitney *U*-test was applied to continuous variables that did not meet these criteria. Among these, three variables with a Gaussian distribution and four variables without a Gaussian distribution demonstrated statistically significant differences between the FA and FTC groups (Figure 2 and Supplementary Table 2). The three variables that followed a Gaussian distribution were the white blood cell count (WBC, p<0.001), albumin (ALB, p=0.003), and mean corpuscular hemoglobin concentration (MCHC, p=0.025). The four variables that did not meet the criteria for a Gaussian distribution or homogeneity of variance were direct bilirubin (DBIL, p=0.004), total bilirubin (TBIL, p=0.014), lymphocyte count (LYM#, p=0.011), and red cell distribution width-

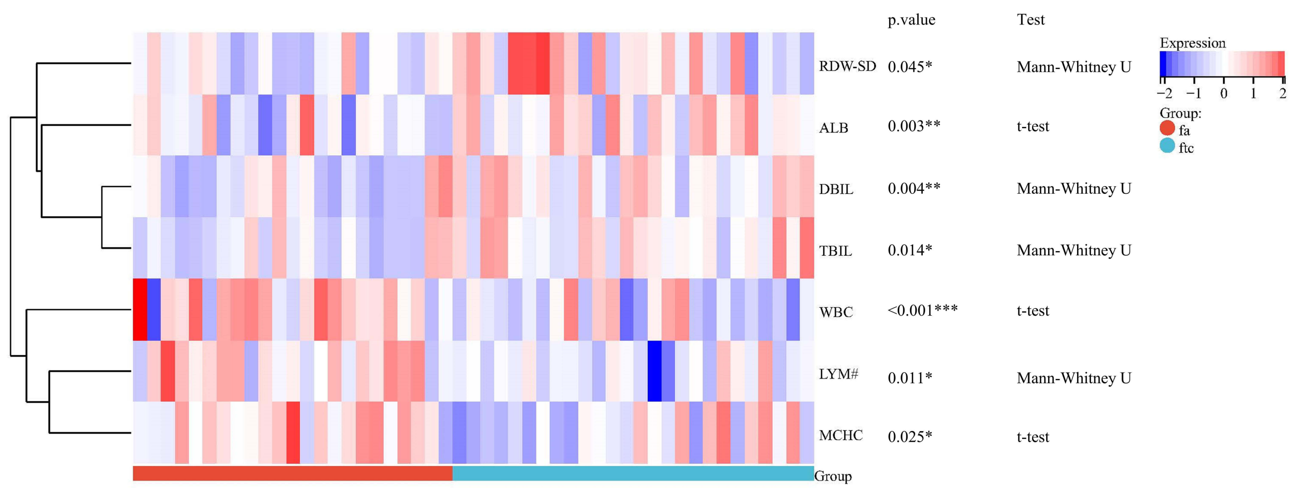

Figure 2 The heatmap of seven blood biomarkers with statistical significance. (*p<0.05, **p<0.01, ***p<0.001).

standard deviation (RDW-SD, p=0.045). It is noteworthy that ALB, RDW-SD, and TBIL exhibited a positive correlation with the presence of FTC, whereas the remaining biomarkers demonstrated a negative correlation.

Construction of the Scoring System

Univariate logistic regression analysis was employed to calculate the odds ratios (OR) and 95% confidence intervals (95% CI) for seven variables (see Table 2 and Figure 3). The analysis revealed statistically significant differences for all seven biomarkers. The results indicated statistically significant differences for ALB (p = 0.009), DBIL (p = 0.020), LYM# (p = 0.010), MCHC (p = 0.033), RDW-SD (p = 0.034), TBIL (p = 0.036), and WBC (p = 0.002). Subsequently, the seven biomarkers were entered into a multivariate logistic regression model.

The subsequent multivariate logistic regression analysis indicated that ALB was positively associated with the incidence of FTC ($\beta = 0.544$, p = 0.038), while WBC was negatively associated ($\beta = -1.101$, p = 0.049). After rounding the two regression coefficients to two significant figures, the predictive formula for FTC was constructed as follows: Score = 0.54 × ALB – 1.10 × WBC.

Performance of the Predictive Model

The median score in the FTC group was higher than that in the FA group (18.724 vs 16.773, p < 0.001) (Figure 4). To evaluate the performance of the seven previously identified biomarkers, receiver operating characteristic (ROC) curves were applied (see Figure 5 and Table 3). In comparison to models comprising a single predictor, the predictive model incorporating ALB and WBC exhibited the greatest area under the curve (AUC) (AUC = 0.839, p < 0.001). The model

Table 2 Logistic Regression Analysis for the Association Between FTC and FA

Variable	Univariate		Multivariate		
	OR (95% CI)	p-value	β value	OR (95% CI)	p-value
ALB	1.492 (1.141,2.110)	**0.0095****	0.544	1.722 (1.105, 3.161)	**0.0379***
DBIL	1.707 (1.131,2.845)	**0.0205***			0.2235
LYM#	0.063 (0.006,0.387)	**0.0095****			0.1302
MCHC	0.942 (0.887,0.991)	**0.0328***			0.7572
RDW-SD	1.253 (1.034,1.585)	**0.0340***			0.0888
TBIL	1.14 (1.022,1.309)	**0.0356***			0.1524
WBC	0.282 (0.114,0.575)	**0.0019****	−1.101	0.332 (0.091, 0.884)	**0.0487***

Notes: Bold font: Significant difference. *p<0.05, **p <0.01.

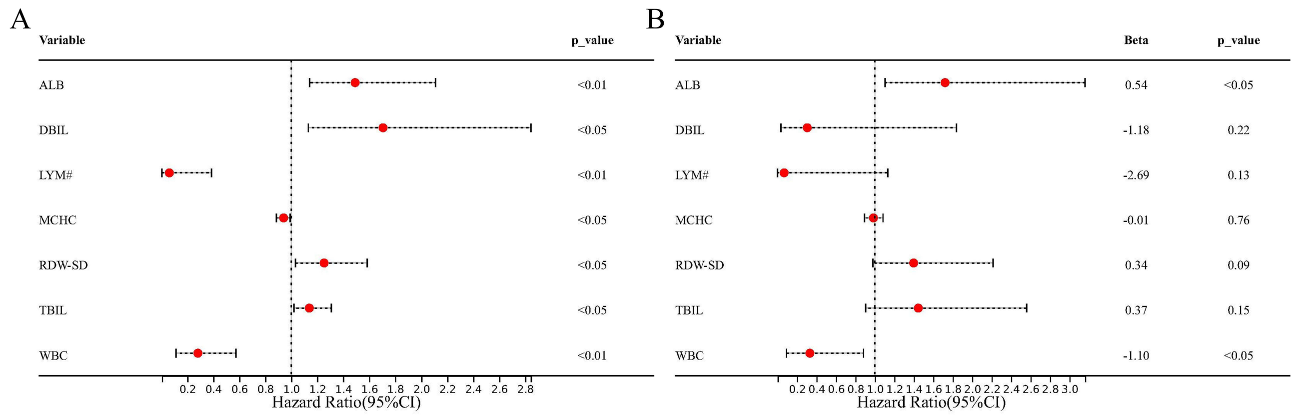

Figure 3 Forest plot of logistic regression of 7 biomarkers. (**A**) Univariate logistic regression. (**B**) Multivariate logistic regression.

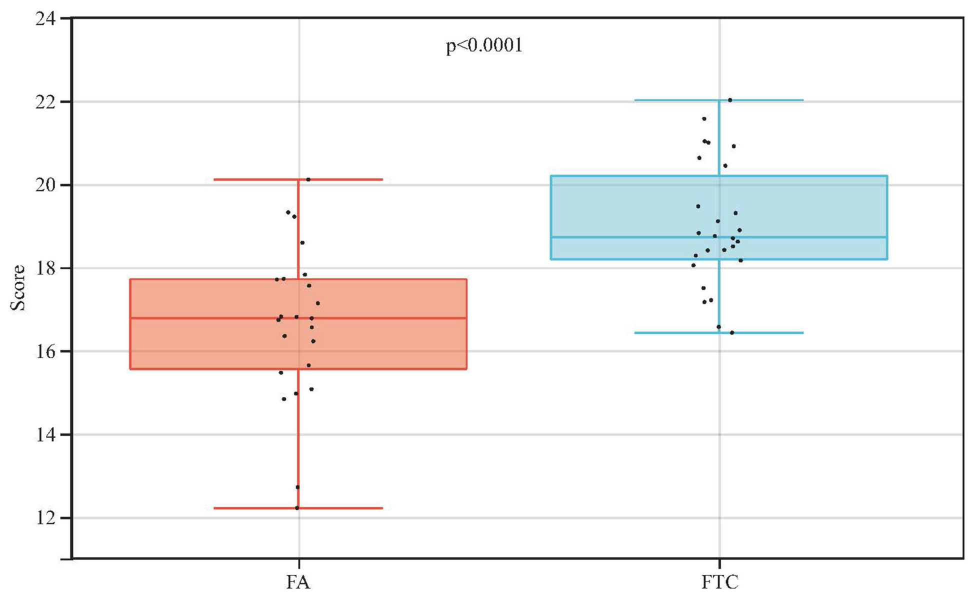

Figure 4 The comparison of scores between the two groups. The medians and interquartile ranges were displayed here. The Mann–Whitney *U*-test was applied.

exhibited optimal predictive accuracy at a cut-off value of 17.935, with sensitivity, specificity, and Youden index values of 0.808, 0.826, and 0.634, respectively.

Discussion

In the majority of cases, patients with suspected thyroid nodules undergo a series of diagnostic procedures, including ultrasound examination, fine-needle aspiration, and cytopathological assessment, to determine whether surgical intervention is necessary. Before initiating medical intervention, a battery of routine tests is conducted to assess the patient's general health status, including a complete blood count (CBC), CMP, thyroid function tests, and coagulation tests. This study identified seven biomarkers associated with FTC out of 317 blood biomarkers. Among them, ALB, DBIL, and TBIL can be assessed through CMP, while WBC, LYM#, and RDW-SD are routine parameters in CBC. Notably, none of the biomarkers from preoperative thyroid function tests were found to be associated with FTC.

A predictive model was developed through retrospective analysis to differentiate between FA and FTC. The model was constructed using multiple blood biomarkers, with ALB and WBC identified as the main predictors. The model

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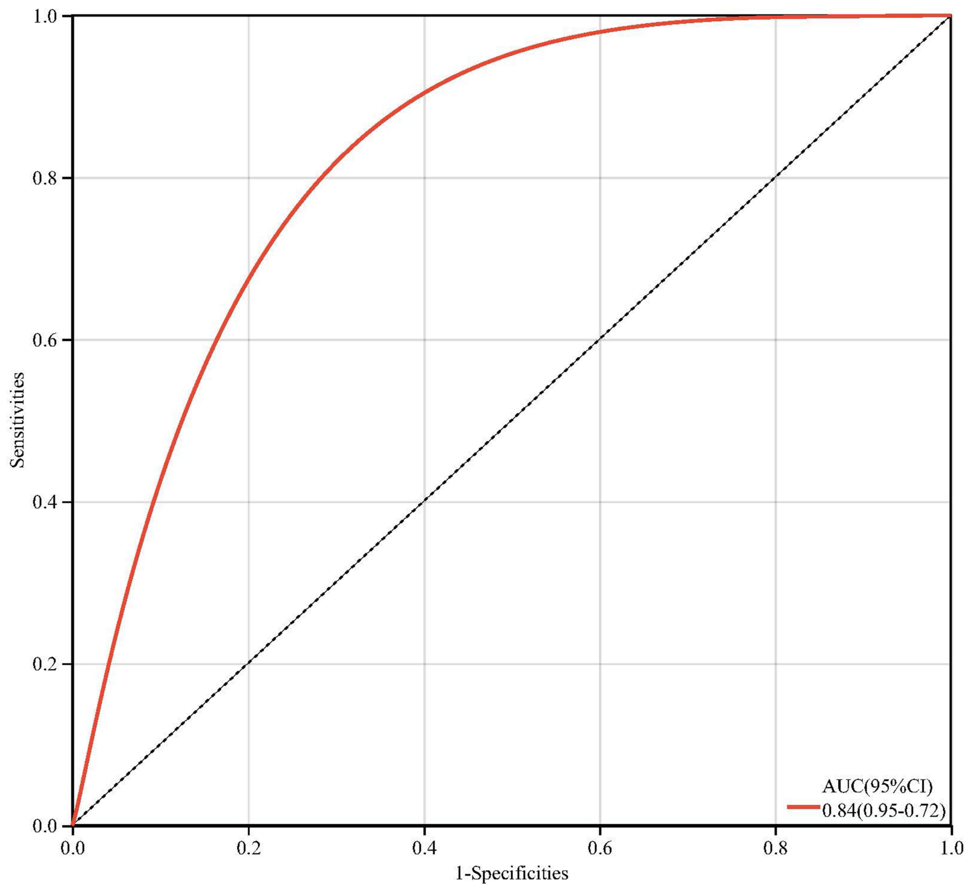

Figure 5 The ROC curve of the scoring system.

demonstrated good predictive performance, with an AUC of 0.839. This indicates that ALB and WBC have significant clinical value in the diagnosis and risk assessment of FTC.

ALB is widely regarded as a critical biomarker for assessing nutritional status and inflammation. Its levels are closely linked to the development and progression of various malignancies, including hepatocellular carcinoma (HCC) and FTC. In the case of HCC, elevated ALB levels have been shown to inhibit tumor metastasis and invasion by modulating the expression of urokinase-type plasminogen activator receptor (uPAR) and matrix metalloproteinases (MMP2 and MMP9).[27] ALB's role in other cancers, such as FTC, is more complex. In response to tumor-induced stress, ALB

Table 3 Predictive Accuracy of the Blood Markers and the Scoring System Based on the ROC Curve

Variable	AUC	p-value	Cut-off Value	Sensitivity	Specificity	Youden Index
WBC[a]	0.8	**<0.001*****	5.77	0.692	0.652	0.344
ALB	0.732	**0.005****	44.75	0.577	0.652	0.229
DBIL[a]	0.742	**0.004****	3.85	0.577	0.696	0.273
LYM#[a]	0.713	**0.011***	1.775	0.692	0.652	0.344
TBIL	0.706	**0.014***	12.6	0.654	0.696	0.35
MCHC	0.663	0.051	331.5	0.654	0.609	0.263
RDW-SD	0.668	**0.044***	40.85	0.577	0.652	0.229
Score	0.839	**<0.001*****	17.935	0.808	0.826	0.634

Notes: Bold font: Significant difference. *p<0.05, **p<0.01, ***p<0.001. [a]WBC, LUM# and DBIL were negatively correlated with the FTC. Hence their AUCs were calculated on the condition that the control group was defined as the state variable.

synthesis may increase as a compensatory mechanism to maintain plasma protein levels and nutrient supply, potentially reflecting the body's adaptive response to tumor progression.[28,29]

Moreover, ALB possesses antioxidant properties that may reduce tumor aggressiveness by mitigating oxidative stress in the tumor microenvironment, particularly in the early stages. However, it is important to recognize that lower ALB levels are often associated with inflammation, which can be triggered by acute inflammatory markers like C-reactive protein (CRP). In FTC, for instance, the inflammatory response may be less pronounced compared to other cancers, such as FA or precancerous lesions.[30–33] Interestingly, ALB+ cells have been linked to increased malignancy potential, as they often show a consistent correlation with *MKI67*, a marker of cellular proliferation, suggesting that *ALB* may promote tumor cell proliferation.[34]

Furthermore, ALB's role in tumor progression appears to extend beyond mere inflammation regulation. In FTC, tumor cells might influence hepatic ALB synthesis by inducing Kupffer cells in the liver to produce cytokines like IL-1β, IL-6, and TNF.[35,36] These interactions suggest that ALB could play a regulatory role in tumor cell proliferation and adaptation to the microenvironment.[37]

While ALB is an established marker for nutritional and inflammatory status, it also holds significant potential as a prognostic biomarker in cancer. Preoperative ALB levels have been shown to correlate with patient prognosis and provide valuable insights into disease severity. The advantages of using serum ALB as a diagnostic tool in cancer patients are its low cost, high reproducibility, and robust functionality, making it a reliable marker for predicting outcomes in FTC patients.[38–41]

The reduction in WBC levels observed in patients with FTC may be attributed to a decrease in lymphocytes in the blood. As previously stated, the inflammatory response in FA may be more pronounced than in FTC, resulting in discrepancies in WBC between the two groups. Similarly, a study on PTC revealed that WBC levels in PTC patients were significantly lower than those in patients with thyroid nodules accompanied by nodular goiter, which corroborates our findings.[42] Another study on preoperative testicular tumors and systemic inflammatory markers also corroborated the finding that lymphocyte levels in the blood were higher in some patients with benign tumors compared to those with malignant tumors.[43] Lymphocytes play a pivotal role in specific immunity, particularly T cells and natural killer (NK) cells, which combat tumor progression by directly killing tumor cells. In patients with cancer, the normal functions of lymphocytes are often suppressed, which results in an ineffective immune response against tumor growth and metastasis.[44,45] Tumor-infiltrating lymphocytes (TILs) may result in a reduction of peripheral lymphocytes in solid tumors through the expression of immune checkpoint inhibitors (ICPIs), including PD-1, TIM-3, and CTLA-4.[44] Additionally, M2-type tumor-associated macrophages (TAMs) facilitate tumor growth by releasing IL-10 and TGF-β, which impede T cell proliferation and activation, thereby establishing a markedly immunosuppressive microenvironment.[46–48] Some studies have indicated that during clinical visits or follow-ups, patients with more aggressive follicular-derived thyroid cancers are characterized by a reduction in immune effector cells (such as CD4+ T cells, γ-δ T cells, and NK T-like cells), which is consistent with our conclusions.[49]

BIL is a byproduct of hemoglobin degradation that exhibits notable antioxidant and anti-inflammatory characteristics. It has been demonstrated that BIL can play a protective role in the development of cancer by either inhibiting oxidative stress-induced cellular damage or by influencing the tumor microenvironment.[50,51] However, elevated BIL levels have also been linked to an increased risk of certain types of cancer, particularly hematologic malignancies. For example, elevated bilirubin levels have been demonstrated to possess independent prognostic value in patients with diffuse large B-cell lymphoma (DLBCL).[52] The results of this study indicate that patients with FTC exhibited elevated TBIL levels and decreased DBIL levels, suggesting an upward trend in indirect bilirubin (IBIL) in their blood. A multicenter study indicated that IBIL (the primary component of TBIL) was positively correlated with the risk of colorectal cancer (CRC) in men, while inversely correlated in women.[53] These findings suggest that high BIL levels may reflect more complex biological mechanisms in certain types of cancer, beyond its simple antioxidant effects.

Furthermore, a notable elevation in RDW-SD and MCHC was discerned in the FTC cohort. A comparable phenomenon was documented by Arda et al in malignant testicular tumors, which lends further support to our findings.[43] Some researchers have combined RDW with inflammatory markers to develop a risk assessment model for epithelial ovarian cancer, demonstrating good diagnostic efficacy.[17]

Previous studies on the prediction of FTC have primarily concentrated on genetic mutations and imaging. Research has indicated that the most prevalent *FLT3* mutation in FTC may serve as a promising candidate for use as a malignancy marker, while *TP53* and *RET* mutations also exert a significant influence on the development of FTC. A predictive model based on the combination of these three mutations demonstrated an AUC of 0.647.[8] Li et al developed a predictive model that integrated ultrasound characteristics with thyroglobulin (TG) levels to assess the risk of FTC in cases where intraoperative frozen section (IOFS) diagnosis was uncertain for suspected follicular tumors. The model identified five key predictive factors: nodule size, TG level, hypoechogenicity, lobulated or irregular margins, and thick halo.[11] In addition, the Bethesda classification system for fine needle aspiration cytology (FNAC) results has an important role in the diagnosis of thyroid tumors. Bethesda type II usually indicates a benign lesion with a very low probability (about 1.5%) of malignant transformation, while type III represents an atypical or low-risk malignant lesion with a probability of malignancy of about 19.2%.[54,55] This classification can help doctors decide whether to perform further imaging or surgical resection. Studies in recent years have shown a higher rate of malignancy among Bethesda type III patients, and more follow-up and evaluation is needed to detect potentially malignant lesions in a timely manner.[55] Our study demonstrated a positive predictive value of 84.0% and a negative predictive value of 79.2%. Despite the existence of previous research proposing diagnostic models for predicting FTC, these models are frequently based on costly sequencing or existing fine-needle aspiration/operative samples. This renders them less feasible for low-cost preoperative risk assessment, thereby limiting their clinical utility.

The diagnostic model developed in this study, based on routine preoperative blood biomarkers, can accurately predict the risk of FTC in thyroid tumor patients at a low cost without the need for biopsy or surgical samples. The results demonstrate that preoperative ALB levels were markedly elevated in FTC patients, while WBC levels were significantly reduced in comparison to FA patients. These findings provide a compelling biological rationale for the construction of the diagnostic model. In comparison to conventional diagnostic techniques that necessitate fine-needle aspiration or surgical sampling, this model offers notable advantages, including its non-invasive feature, ease of operation, and cost-effectiveness. The model can facilitate rapid and convenient preliminary screening by relying solely on routine preoperative blood test data, thereby reducing patient discomfort, minimizing the risk of complications, and alleviating the financial burden. In contrast to costly imaging tests and surgical diagnostics, this model is not only cost-effective but also adaptable to resource-limited healthcare settings.

This model is particularly well-suited for early screening, enabling clinicians to promptly identify high-risk patients at the initial diagnosis. This improves diagnostic efficiency and prevents disease progression due to diagnostic delays. Furthermore, blood tests are straightforward to perform and highly reproducible, enabling dynamic monitoring of patients preoperatively, postoperatively, and during follow-up, thus supporting ongoing risk assessment, especially to avoid the complications of unnecessary total thyroidectomy.[56,57] This economical, efficient, and non-invasive screening tool provides a novel solution for the early diagnosis of FTC, optimizing the patient care experience and enhancing the utilization of healthcare resources.

It should be noted that this study is subject to several limitations. First, the retrospective study design inherently introduces the potential for selection bias, which may be challenging to avoid. Secondly, this study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the results. Furthermore, the limited number of patients included in this study precludes the evaluation of the predictive model with a validation set. Consequently, future research should aim to increase the sample size and conduct multicenter prospective studies to further verify the reliability and practicality of the model. Additionally, molecular biology experiments are needed to explore the specific mechanisms of ALB and WBC in FTC, to better understand the clinical value of these biomarkers. The presence of other malignant neoplasms in FA merits consideration, thereby restricting the applicability of this model to a certain degree. Nevertheless, it retains significant clinical value, particularly in terms of reducing the number of unnecessary surgical procedures and diagnostic tests.

Conclusion

In conclusion, to the best of our knowledge, this study is the first to develop a predictive model based on the relationship between routine blood biomarkers and FTC. The model utilizes ALB and WBC to effectively distinguish between FA and FTC, demonstrating significant clinical potential. Further multicenter studies and mechanistic exploration may prove beneficial in optimizing and promoting this model, which could facilitate early diagnosis and personalized treatment of thyroid tumors.

Abbreviations

FTC, follicular thyroid carcinoma; FA, follicular adenoma; PTC, papillary thyroid carcinoma; CMP, comprehensive metabolic panel; BIL, bilirubin; DBIL, direct bilirubin; TBIL, total bilirubin; IBIL, indirect bilirubin; ALB, albumin; WBC, white blood cell count; LYM#, lymphocyte count; RDW-SD, red cell distribution width-standard deviation; MCHC, mean corpuscular hemoglobin concentration; ROC, receiver operating characteristic; AUC, area under the curve; CRP, C-reactive protein; CBC, complete blood count; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastasis; DLBCL, diffuse large B-cell lymphoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; uPAR, urokinase-type plasminogen activator receptor; MMP, matrix metalloproteinase; TILs, tumor-infiltrating lymphocytes; ICPIs, immune checkpoint inhibitors; TAMs, tumor-associated macrophages; IL, interleukin; TGF, transforming growth factor; TG, thyroglobulin.

Data Sharing Statement

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study has been approved by the Ethics Committee of Renmin Hospital of Wuhan University (NO. WDRY2024-K038). The requirement for obtaining informed consent from the involved patients was waived due to the retrospective nature of the study design.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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