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Coagulation and thyroiditis are factors associated with adverse pathological features in differentiated thyroid cancer: a retrospective cohort study

Xiao Chen[1,2], Han-yu Wang[1,2†], Lu Yu[1,2†], Jia-qi Liu[1,2] and Hui Sun[1,2*]

Abstract

Objective Lymph node metastasis (LNM) and thyroid capsular invasion (CI) are the main pathological features leading to poor prognosis of differentiated thyroid cancer (DTC), and there is a lack of effective diagnostic methods before surgery. Therefore, this study was designed to analyze a large number of preoperative clinical features of DTC and identify factors closely related to those two pathological features.

Methods 4557 patients with DTC, postoperative pathological results showed LNM in 2146 cases and CI in 2783 cases were retrospectively included. The preoperative blood, urine, serum laboratory test and ultrasound of thyroid were performed for data collection. A total of 74 clinical features were analyzed by the methods of principal component analysis (PCA), and key principal components were extracted for regression analysis of LNM and CI as well as subgroup analysis.

Results 11 key clinical features were used for principal component analysis, and 6 principal components PC0-PC5 were finally obtained. PC0 is mainly composed of prothrombin time and international normalized ratio, and the score represents better coagulation function and has a protective effect on LNM. PC1 is mainly composed of thyroid peroxidase antibody and thyroid texture, and the score represents the severity of thyroiditis and has a protective effect on LNM and CI.

Conclusion Thyroiditis and coagulation function were identified by principal component analysis as protective and risk factors for adverse pathology of DTC, meaning they were closely related to tumor metastasis and invasion.

Keywords Differentiated thyroid cancer, Coagulation, Thyroiditis, Metastasis, Invasion

†Xiao Chen and Han-yu Wang contributed equally to this work.

*Correspondence:
Hui Sun
sunny68@hust.edu.cn
[1]Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 JieFang Avenue, Wuhan, Hubei 430022, P.R. China
[2]Hubei Medical Clinical Research Center for Diabetes and Metabolic Diseases, Wuhan 430022, China

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Introduction

Thyroid neoplasms are common malignancies of the endocrine system, with differentiated thyroid cancer (DTC) accounting for more than 95% of all tumor incidences [1, 2]. Distinct from other systemic neoplastic diseases, DTC usually have a relatively favorable prognosis and rarely develop distant metastases. At present, the pathological features of DTC with significant correlation with prognosis are mainly reflected in local lymph node metastasis of the tumor, as well as extrathyroidal invasion of the tumor tissue after breaking through the thyroid capsule [3]. When combined with these two types of pathologic features, such tumors tend to be considered to have worse pathologic stage. Because studies have shown that such tumors are more likely to recur after surgery, or have a risk of further distant metastasis, and affect patient survival [4, 5]. Therefore, prompt surgical treatment of such tumors is required, and the extent of surgical resection is adjusted according to the status of local tumor metastasis or invasion [6].

Because of the indolent characteristics of thyroid tumors, there is still a lack of diagnostic modalities or biomarkers that can make direct predictions about the adverse pathological features of DTC [7]. In some clinical retrospective studies, it was found that metastasis and invasion of DTC may be associated with some baseline clinical characteristics of patients, and artificial diagnostic tools, such as predictive models, were developed based on these characteristics, which somewhat improved the preoperative predictive power for pathological features of DTC [8]. However, such studies included relatively single data types, and most of them predicted the actual pathological status of thyroid tumors or nodules by screening their imaging features under ultrasound. Ultrasound localization and characterization, on the other hand, are very dependent on the subjective experience of the operator and are not fully representative [9, 10]. Therefore, prognostic factors other than ultrasound in thyroid tumors remain elusive. In particular, biochemical markers of other systems than the thyroid gland, may also have potential pathogenic or protective effects on the pathological and prognostic characteristics of tumors [11].

Therefore, we included postoperative cases of larger patients with thyroid tumors in this study and mainly collected clinical data other than local ultrasound morphology of thyroid tumors. Including a number of laboratory tests of blood and urine samples of patients, combined with general epidemiological characteristics, the main risk factors for poor prognosis of thyroid tumors were explored by means of data dimension reduction using principal component analysis (PCA).The primary objective of this study is twofold: to establish a clinical foundation for elucidating the pathological mechanisms responsible for invasion and metastasis in differentiated thyroid carcinoma (DTC), and to provide novel reference parameters for predicting adverse pathological characteristics.

Materials and methods

Study cohort and examination indicators

The retrospective cohort selected for this study included all patients who were hospitalized in Wuhan Union Hospital due to DTC and underwent thyroidectomy and lymph node dissection from 2018 to 2021. All patients had confirmed postoperative pathological diagnoses, including documentation of capsule invasion (CI) and lymph node metastasis (LNM).In our study, patients diagnosed with DTC in either lobe through intraoperative frozen section analysis underwent prophylactic central lymph node dissection (CLND) on the affected side(s). Therefore, the lymph node metastasis (LNM) referred to in this study primarily indicates central lymph node metastasis. Patients with potential confounding factors were excluded from the analysis, including those with: (1) previous thyroid-related surgeries performed at other institutions; (2) current use of thyroid-related medications; (3) history of major systemic diseases with current use of potentially interfering medications (e.g., anticoagulants) that may affect preoperative laboratory results. A total of 4557 patients were included, including 2146 patients with lymph node metastasis and 2783 patients with capsular or extrathyroidal invasion of thyroid tumors. The most recent clinical examination prior to surgery was collected for these patients. Including blood cell count, biochemical and endocrine related tests, urine tests and thyroid ultrasound examination, a total of 74 examination items. Subsequent statistical analyses were performed on these data. This study was approved by the institutional review board of the Wuhan Union Hospital, and the requirement for informed consent was waived.

Statistical analysis

Principal component analysis

We normalized the data as well as principal component transformation for 74 clinical features and 2 pathological features after performing multiple imputation and obtained 76 principal components. The principal component set (minor principal component set) at the end and the principal component set (major principal component set) at the front end were screened according to the elbow graph and principal component weight graph, respectively. The scores of these principal components were analyzed for clinical correlation with all raw data, and the variables that best represented the structure of the raw data were selected for analysis based on the significance of the correlation (p-value less than 0.05) between each clinical feature and each principal

component in the minor principal component set and the major principal component set. For example, when a clinical feature has a significantly larger number of principal components associated with it in the principal component set than in the minor principal component set, the feature is retained and vice versa is removed. We used this approach to screen the original clinical features twice. Finally, the clinical features that best represent the original data features are retained for the final data dimension reduction, and the key principal components after dimension reduction are obtained.

Clinicopathological correlation analysis

Principal component score after principal component analysis was used as a new clinical feature, and multiple logistic regression analysis was performed with lymph node metastasis and thyroid capsular invasion as two pathological conditions, respectively, after matching the two confounding factors of age and gender to determine the correlation between these principal components and the prognosis of thyroid cancer. Similarly, the weights occupied by the original clinical features in each principal component were determined based on spearman correlation coefficient and pearson correlation coefficient using batch clinical correlation tests. These original clinical features were further examined as independent risk or protective factors for pathological conditions in the original data. Finally, subgroups were differentiated by sex and age, and subgroup analyses of clinical versus pathological characteristics were performed in the subgroup population.

The statistical analysis process were completed by python 3.8, R 4.3.1, SPSS 26.0, and p-values less than 0.05 were considered statistically significant.

Results

Baseline data

The raw data for this study cohort contained a total of 74 clinical features as well as 2 pathological features. Pathologic features as dependent variables were lymph node metastasis and thyroid capsule invasion. The details included in the clinical features are shown in Table S1. After principal component analysis and factor screening of these clinical characteristics, a total of 11 indicators were finally included in the analysis. Their distribution with age and sex in populations with different pathological characteristics is shown in Table 1.

Factor screening and dimensionality reduction

Because the clinical features covered by the original data were too redundant, we screened all 76 features twice by principal component analysis. After the first principal component transformation, 76 features were transformed into 76 principal components, and their weights on the original data are shown in Fig. 1-A and -B. According to this result, 16 minor principal components at the tail of the elbow graph and principal component weight graph, as well as 16 principal components at the head, were screened as minor principal component sets as well as major principal component sets, respectively. Each principal component in the set was correlated with each clinical feature of the original data, and the number of principal components that were significantly correlated

Table 1 Baseline data of all clinical characteristics screened for principal component analysis

	LNM(*n* = 2146)	No LNM(*n* = 2411)	CI(*n* = 2783)	No CI(*n* = 1774)
Albumin/globulin ratio	1.70(1.50–1.90)	1.70(1.50–1.90)	1.70(1.50–1.90)	1.70(1.50–1.90)
Lactate dehydrogenase(U/L)	183(159–209)	186(162–212)	184(160–210)	186(160–212)
Prothrombin time(s)	12.60(12.30–13.10)	12.60(12.20–13.00)	12.60(12.20–13.00)	12.60(12.20–13.00)
Activated partial thromboplastin time(s)	36.40(34.20–38.70)	36.00(34.00-38.40)	36.30(34.10–38.70)	36.10(34.10–38.30)
Parathyroid hormone(pg/ml)	56.00(40.20–74.00)	58.70(43.20-75.58)	56.70(41.60-74.24)	58.40(42.60–75.50)
International normalized ratio	0.96(0.92-1.00)	0.96(0.92–0.99)	0.96(0.92-1.00)	0.96(0.92-1.00)
Platelets(10^9/L)	235(198–275)	232(193–273)	233(196–274)	234(195–273)
Neutrophil ratio(Neu%)	59.40(53.10–65.20)	59.10(53.20–65.00)	59.30(53.39–65.40)	59.15(52.90-64.78)
Thyroid peroxidase antibody(U/ml)	1.00(1.00-13.16)	1.00(1.00-20.55)	1.00(1.00-13.90)	1.02(1.00-22.06)
Thyroid stimulating hormone(mIU/L)	1.79(1.25–2.61)	1.81(1.25–2.66)	1.82(1.28–2.67)	1.77(1.17–2.60)
Age(years)	52(40–52)	52(45–52)	52(43–52)	52(42–52)
Texture of thyroid(n%)				
Homogeneous	528(24.60%)	731(30.32%)	729(26.19%)	799(45.04%)
Inhomogeneous	1025(47.76%)	1073(44.50%)	1300(46.71%)	529(29.82%)
Missing data	593(27.64%)	607(25.18%)	754(27.00%)	446(25.14%)
Gender(n%)				
Male	644(30.01%)	434(18.00%)	693(24.90%)	385(21.70%)
Female	1502(69.99%)	1977(82.00%)	2090(75.10%)	1389(78.30%)

Abbreviation: LNM Lymph Node Metastasis, CI Capsular Invasion

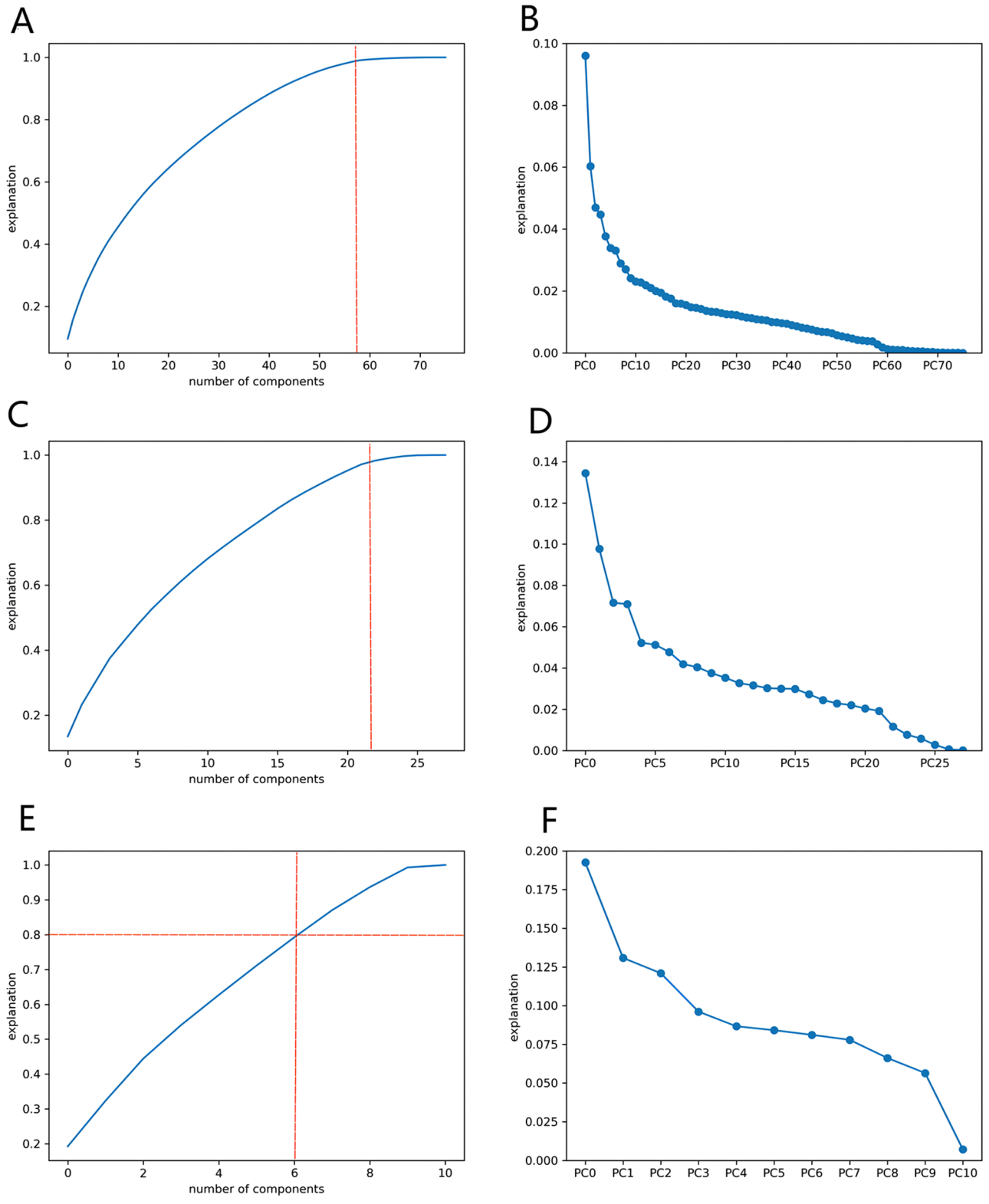

Fig. 1 Elbow diagram and principal component weight diagram for dimension reduction of data by principal component analysis. (1-**A**, **B**) 76 principal components were entered and principal components from PC60 onwards were classified as minor principal components. (1-**C**, **D**) Twenty-eight principal components were entered and principal components from PC22 onwards were classified as minor principal components. (1-**E**, **F**) 11 principal components are input, and finally the first 6 principal components (PC0-PC5) whose cumulative explanation reaches 0.8 are selected as the final dimension reduction results

with each clinical feature in the two principal component sets was compared. This result is shown in Figure S1A-F. Finally, a larger number of clinical features significantly associated with each principal component in the primary principal component set were retained for secondary principal component screening. This process screened 28 clinical features and repeated the first screening process. After the second principal component transformation, the principal component weights corresponding to 28 clinical features are shown in Fig. 1-C and -D. According to this result, the first 6 principal components and the last 6 principal components were analyzed as the primary and secondary principal component sets for correlation matrix with clinical characteristics, and the results of this analysis are shown in Figure S2A-F. 11 clinical features were finally selected as the most representative variables for the original data structure for subsequent analysis.

Principal component analysis and clinicopathologic correlation analysis

Dimensionality reduction of principal components was performed again after screening 11 key clinical features. The results of Fig. 1-E and -F showed that there were no more principal components at the ends of these 11 principal components that contributed ineffectively to the original data feature degree, indicating that the previous two feature screens yielded good results. Therefore, we chose the first six principal components PC0-PC5 that contributed 80% to the original data structure as the results after data dimension reduction. These 6 principal components were correlated with 11 clinical features, and the clinical features with significant correlation were selected to assess the clinical feature dimension mainly represented by each principal component according to the magnitude of the correlation coefficient. The results of Fig. 2-A showed that PC0 was mainly associated with Prothrombin time (PT) and International normalized ratio (INR), representing coagulation function. Figure 2-B suggests that PC1 is mainly associated with Thyroid peroxidase antibody (ATPO) and thyroid texture, representing thyroiditis. We further performed multiple logistic regression between the scores of these principal components and the two pathological features, and found that after including both confounding factors, age and gender,

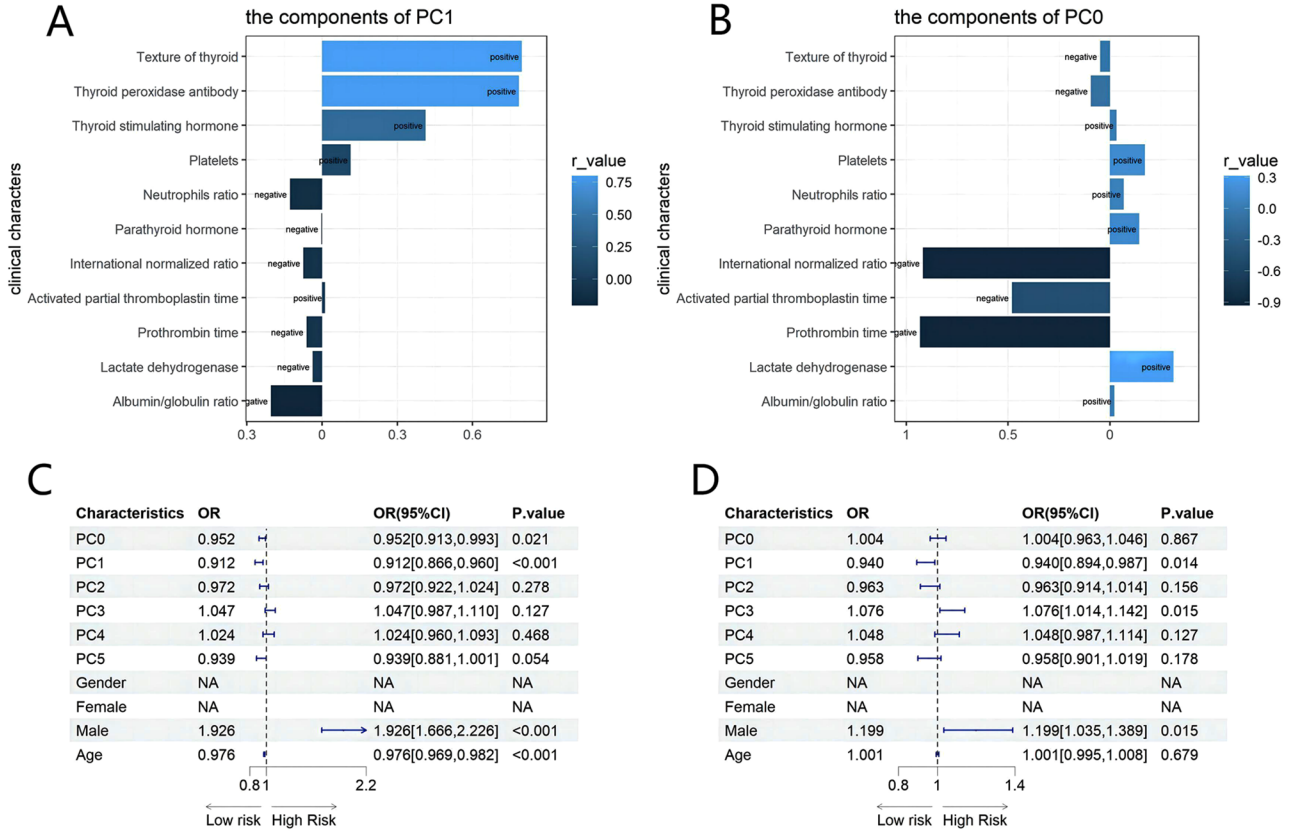

Fig. 2 Abbreviation: LNM Lymph nodes metastases, CI Capsular invasion. Weight plot of correlation coefficients between two principal components PC1, PC0 and 11 clinical features (2-**A**, **B**). r value is pearson 's correlation coefficient for continuous variables and spearman' s correlation coefficient for categorical variables. Absolute values of r value greater than 0.7 were considered strongly correlated with principal components. Forest plot of multiple logistics regression between six principal components (PC0-PC5) combined with age, gender and two pathological features LNM (2-**C**), CI (2-**D**). $p < 0.05$ was considered an independent risk factor

Fig. 2-C indicated that PC0 and PC1 were associated with lymph node metastasis and showed a significant protective effect on the occurrence of lymph node metastasis. Figure 2-D suggests that PC1 and PC3 are associated with thyroid capsule invasion, PC1 is a protective factor, and PC3 is a risk factor.

Subgroup analysis

To further validate the results of principal component analysis. We again performed multiple logistic regression based on pathological features for 11 clinical features and simultaneously matched age and gender factors. Figure 3A-B suggests that thyroiditis as well as coagulation parameters such as PT, ATPO, and INR still have a significant effect on the development of pathological conditions, consistent with the results of principal component analysis. We then divided the original population into two subgroups according to sex. At the same time, we performed a restrictive cubic spline (RCS) analysis of the age of the patients, and the results of Figs. 4-A and 4-B suggest that as continuous variables, age around 52 years is more suitable for stratifying patients because the role of age on disease prognosis changes before and after this value. Patients were divided into older and younger groups by 52 years of age. Multiple logistic regression of PT, ATPO, and INR was repeated in different gender and age subgroups, and Fig. 4-C and 4-D showed that PT and ATPO had a more significant effect on LNM in female patients and younger patients compared with male patients and older people. However, the effect of ATPO on CI showed the opposite trend in male and female patients. Figure 4-E finds that INR no longer significantly contributes to CI after differentiating age and gender subgroups.

Discussion

Because of the indolent nature of DTC, it may be difficult to identify unique risk factors associated with prognosis in previous single index or small sample clinical studies [12]. With the help of data dimension reduction in machine learning-unsupervised learning, we repeated the comparison of 74 clinical features in the original data according to data heterogeneity and the representativeness of the primary and secondary principal component scores after principal component analysis, and finally selected 11 clinical features that were relatively the most representative of the structural features of the original data for the final analysis. These clinical features mainly cover coagulation function, thyroid and systemic inflammatory indicators, thyroid-related endocrine function and so on. Following the final principal component analysis, we identified that principal components representing both coagulation parameters and thyroid immune function were significantly associated with two poor prognostic indicators: thyroid tumor lymph node metastasis and thyroid capsule invasion. After adjusting for age and sex through multiple logistic regression - both established confounding factors in tumor prognosis according to previous studies [13, 14] - the principal component scores maintained significant associations with these pathological features.

According to our results, there was a significant negative correlation between the score of PC0, the principal component representing coagulation function, and the specific coagulation parameters PT and INR. PC0 was also an independent protective factor for lymph node metastasis status in thyroid tumors. demonstrated that prolonged coagulation time is a risk factor for lymph node local metastasis in thyroid tumors. This conclusion

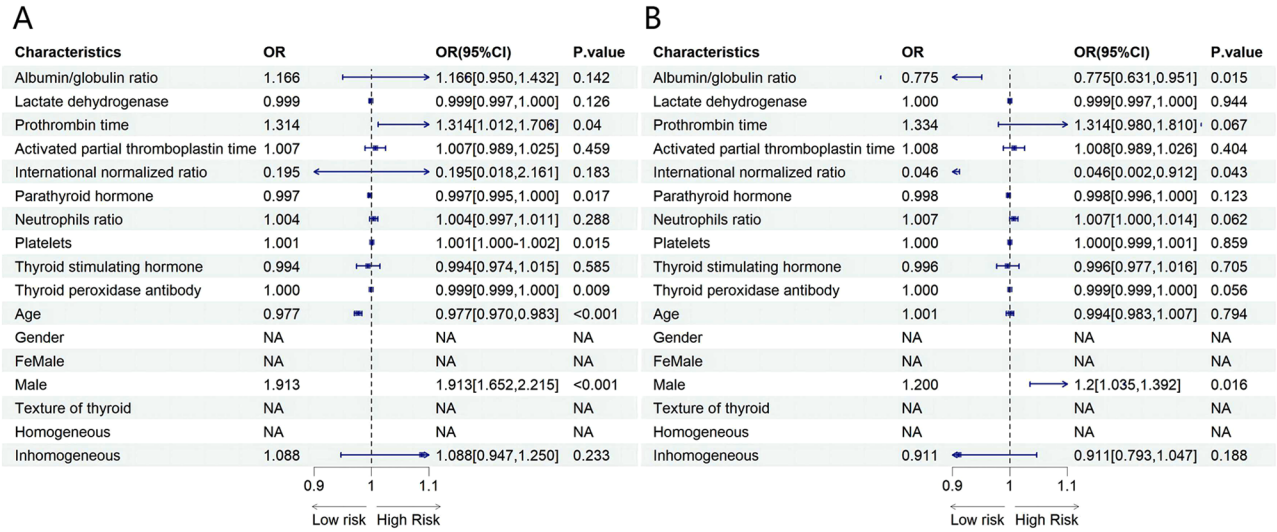

Fig. 3 Abbreviation: LNM Lymph nodes metastases, CI Capsular invasion. Forest plot of multiple logistics regression of 11 clinical characteristics versus age and gender on two pathological characteristics LNM (3-**A**) and CI (3-**B**). $p < 0.05$ was considered an independent risk factor

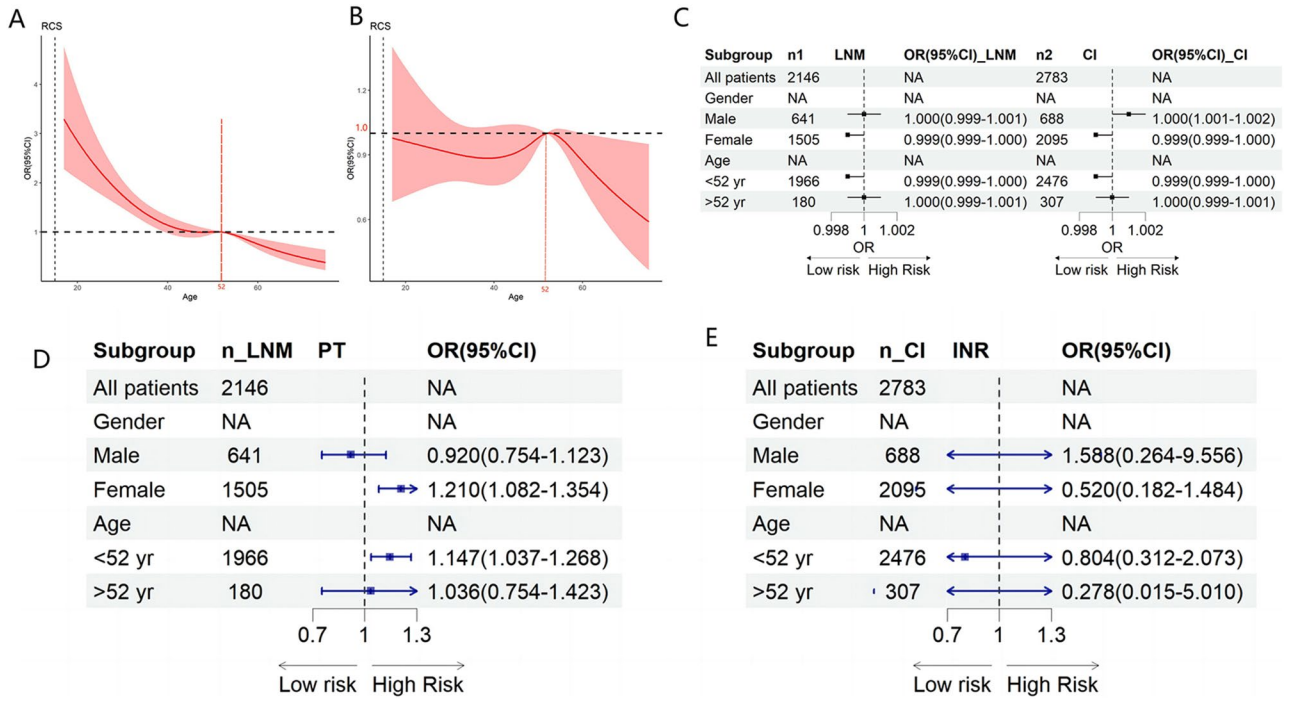

Fig. 4 Abbreviation: LNM Lymph nodes metastases, CI Capsular invasion. Restrictive cubic spline (RCS) plots of age versus LNM (4-**A**), CI (4-**B**), respectively. Multiple logistics regression of ATPO (4-**C**), PT (4-**D**), and INR (4-**E**) on the two pathological conditions in different gender and age subgroups, respectively. Covariates included age, gender, PT (dependent variable LNM), INR (dependent variable CI) for ATPO, age, gender, ATPO for PT (dependent variable LNM), and age, gender, ATPO for INR (dependent variable CI)

was also demonstrated in our original data. Apart from individual studies that have used coagulation parameters as an indicator to predict thyroid tumors to establish prediction models, there has been little previous literature reporting a direct association between coagulation function and thyroid tumor prognosis [15]. However, the results of multiple logistics regression have excluded the possibility of collinearity and confounding factors. Therefore, we consider that it may be similar to the mechanism of other cancers, and the prolongation of coagulation time is more conducive to the establishment of excess blood supply by the local microenvironment of thyroid tumors, which in turn facilitates tumor growth as well as metastasis [16, 17]. This may also serve as a novel indicator to assess whether DTC may have adverse pathology, however, deeper mechanisms may need to be further confirmed by prospective studies or basic studies.

Abnormal thyroid immune function is mainly characterized by elevated thyroid autoantibody titer levels, that is, the occurrence of Hashimoto 's thyroiditis. In our study, two indicators representing thyroid immunity, namely the level of ATPO and whether thyroid ultrasound texture was uniform, were mainly included after principal component dimension reduction screening. Both measures represent the overall immune status of the thyroid gland and are not thought to be altered by tumor effects. In fact, there have been many similar studies on the relationship between the immune status of the thyroid gland and thyroid nodules as well as thyroid tumors. Most studies have shown that Hashimoto 's thyroiditis has a "bidirectional" effect on thyroid tumors, on the one hand, as a risk factor for thyroid tumorigenesis, and on the other hand, as a protective factor for further tumor metastasis or progression after thyroid tumors have formed [18, 19]. The mechanism behind this is not clear and may be considered to be associated with the regulation of the local immune microenvironment of the thyroid [20, 21]. In our study, both PC1 score, which represents the principal component of thyroid immunity, and thyroid immunity index in the original data suggest a protective effect against tumor metastasis and thyroid capsule invasion, which is consistent with most previous studies. This further illustrates the need to pay attention to the specific population of DTC with Hashimoto 's thyroiditis and develop individualized diagnosis and treatment strategies in the future.

Our findings also provide some other interesting findings, such as the association of immune-related and coagulation-related principal components with pathological features seems to be more significant in female patient populations and younger patient populations younger than 52 years after further differentiation of subgroups according to age and sex in the original population. Of course, this may be associated with uneven sample sizes.

However, consistent with previous studies of thyroid cancer risk prediction in this specific population, our results also suggest that more attention should be paid to screening for indicators related to specific populations to better serve a guiding role in clinical practice [22, 23]. In addition, in addition to PC0 and PC1, there are some other principal components and the main clinical features they represent that somewhat suggest an association with thyroid tumors. For example, the neutrophil ratio represented by PC5 and the globulin ratio represented by PC3 also seem to predict a specific relationship between systemic immune status and adverse pathology of DTC. Platelet count and PTH levels, on the other hand, also suggest an association with thyroid tumor invasion and metastasis, respectively. These features have also been reported in some studies because the systemic immune and hematologic conditions are very complex, so they may similarly be reflected in the local microenvironment of thyroid, especially thyroid tumors, through specific pathways or mechanisms [24, 25].However, in our study, the contribution of these indicators to principal components and the association with pathological features was not as significant as that of coagulation and thyroid immunity, and more meticulous matching and correction may be needed to clarify this conclusion.

Our study has limitations because as a retrospective study, bias during data collection cannot be avoided. However, since the purpose of hospitalization for patients with DTC is very clear, no other treatment except surgery will be performed, and there are few complications, we believe that the study results are credible.

Conclusion

After preoperative screening of patients for multidimensional clinical features, thyroiditis and coagulation abnormalities were identified by principal component analysis as independent protective and risk factors for adverse pathology of DTC, meaning they were closely related to tumor metastasis and invasion. It is necessary to validate the relevant indicators at the mechanistic level to help us provide a deeper understanding of the immune-related mechanisms of DTC and the role of the tumor microenvironment and develop accurate diagnosis and treatment strategies for DTC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-025-02898-6.

Supplementary Material 1: Figure S1: Heatmap of the clinical correlation of 74 clinical characteristics with principal component scores after the first principal component analysis. (S1-A, B, C, D) Association of the first 16 major principal component collections (PC0-PC15) with each clinical feature. (S1-E, F, G, H) Association of the post-16 minor principal component collections (PC60-PC75) with each clinical feature. Numbers are p-values indicating whether there is a significant association between clinical characteristics and principal components.

Supplementary Material 2: Figure S2: Heatmap of the clinical correlation of 28 clinical characteristics with principal component scores after the second principal component analysis. (S2-A, B, C) Association of the first 6 major principal component collections (PC0-PC5) with each clinical feature. (S2-D, E, F) Association of the post-6 minor principal component collections (PC22-PC27) with each clinical feature. Numbers are p-values indicating whether there is a significant association between clinical characteristics and principal components.

Supplementary Material 3: Table S1: All clinical characteristics collected and used for principal component analysis and factor screening were included in this study. The number included in each category of clinical features or the abbreviated form of a specific measure is described in parenthesis. These abbreviated forms are also used in the results of the clinical relevance matrix.

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Author contributions

All authors made substantial contributions to the conception and design of this study. XC performed the data analyses and wrote the manuscript; HYW performed the data collection and prepared the manuscript. HS contributed to the conception of the study and provided professional comments on the content. LY and JQL helped with data collection.

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Data availability

Data is provided within the manuscript or supplementary information files.To ensure privacy, raw data can be obtained from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki. This study was approved by the institutional review board of the Wuhan Union Hospital, and the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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