

**A nomogram model to predict central lymph node metastasis in
thyroid papillary carcinoma suitable for primary hospitals**

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Study Protocol and Statistical Analysis Plan

Collection of Patients

1000 Patients who underwent total thyroidectomy or lobectomy and were diagnosed as PTC by pathological examination between June 2014 and September 2019 in Sun Yat-sen Memorial Hospital (Guangzhou, South China) and 200 patients in the First Affiliated Hospital of Zhengzhou University (Zhengzhou, North China) from March 2019 to November 2020 were selected as the subjects to construct the nomogram. The inclusion criteria were as follow: (1) underwent TC operation for the first time; (2) confirmed as PTC by postoperative pathological examination; (3) underwent ipsilateral or bilateral CLND. The exclusion criteria included: (1) complicated with other subtypes of TC or thyroid metastatic cancer; (2) received preoperative interventional therapy (such as radiofrequency and microwave therapy) or head and neck radiotherapy. the patient recruitment process was showed in Figure1. We randomized them at 7:3 and divided it into a training set and a verification set. Besides, 200 cases that met the inclusion and exclusion criteria above-mentioned in the First affiliated Hospital of Zhengzhou University were enrolled as a external verification set.

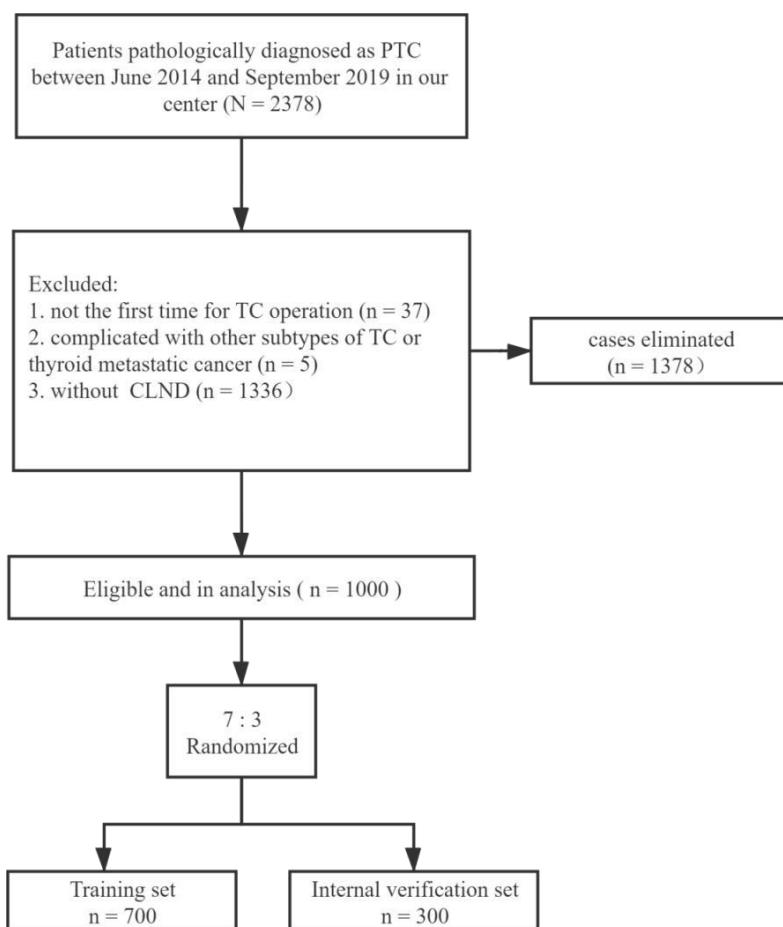


Fig 1. the recruitment process of patients in our study

Surgical Quality Control

All surgeries were conducted by at least two experienced surgeons. According to the preoperative US, all patients in our study underwent total thyroidectomy or lobectomy plus ipsilateral or bilateral CLND and then all specimens were for paraffin fixation and histological analysis in the department of pathology.

Baseline Characteristics

The following clinical features for each patient were obtained before surgery: gender, age, occupation, complicated with autoimmune diseases (absent / present), history of radiation exposure (absent / present), family history of thyroid cancer (absent / present), with other tumors (absent / present) and preoperative laboratory examinations including neutrophil count, lymphocyte count, platelet count, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb).

Preoperative US signatures of thyroid tumors were also included: distribution (unilateral / bilateral), shape (regular / irregular), maximum diameter, number (single / multiple), boundary (clear / semiclear / unclear), component (solid /cystic-solid), calcification (absent / microcalcification / macrocalcification), blood flow (absent / internal / annular), cervical lymph node enlargement (absent / present).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 25.0 and RStudio software. All tests were two-tailed, and a two-sided value of $P<0.05$ was considered statistically significant. The continuous variables for normally distributed data are presented as the mean \pm standard deviation (SD) and were compared by using the Student's t-test. For the variables with a skewed distribution, data are presented as medians (interquartile ranges). The categorical variables are reported as frequencies (percentages), and the characteristics of the patients were compared by using the chi-square test. A least absolute shrinkage and selection operator (LASSO) regression analysis conducted by using the glmnet R package was applied to identify the important preoperative predictors associated with CLNM in the training set, with the optimal values of the penalty parameter λ determined via 10-fold cross-validation. Multivariate logistic regression analysis were conducted to determine the potential nonlinear association between predictors and the risk of CLNM. Odd ratios (ORs), 95% confidence interval (CI) and probability values were obtained by logistic regression analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to evaluate the accuracy of the nomogram for predicting CLNM. The calibration curve and Hosmer-Lemeshow tests were performed to evaluate the calibration of the nomogram. The decision curve analysis (DCA) was applied to validate clinical utility of the nomogram.

