


Research Article

Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Predicting Thyroid Cancer in Intermediate Category Fine Needle Aspiration Pathology

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Abstract

Context: The management of thyroid nodules with intermediate category of the Bethesda System for Reporting Thyroid Cancer (TBSRTC) is still debatable.

Objective: To investigate the diagnostic accuracy of neutrophil-to-lymphocyte ratio (NLR) in detecting cancer in intermediate TBSRTC categories.

Design: Data of the patients who underwent thyroidectomy between 2012 and 2018 were analyzed retrospectively.

Subjects and Methods: Demographic characteristics, complete blood count, thyroid stimulating hormone (TSH) value, TBSRTC categories and postoperative pathology of the patients were collected. The association with preoperative NLR and postoperative pathology was assessed.

Results: Of 146 patients included in the study, 57 (39%) were in TBSRTC III, IV and V category. The mean NLR in this subgroup was 2.1 ± 0.8 and similar between TBSRTC III, IV and IV groups ($p=0.737$). Thyroid cancer was detected in 38 (66.7%) patients. The mean NLR was 2.4 ± 0.8 in thyroid cancers and significantly higher when compared with patients with benign postoperative pathology (1.6 ± 0.4 , $p=0.014$). There was a significant difference between papillary and follicular cancer; the mean NLR was 2.3 ± 0.8 in papillary cancer and 2.6 ± 0.7 in follicular cancer patients ($p=0.005$). The cut-off value of NLR for predicting cancer at 89% sensitivity and 53% specificity was 1.6 (Area under curve: 0.769, 95% confidence interval: 0.643-0.895, $p=0.001$).

Conclusion: Preoperative NLR is elevated in patients with thyroid cancer in intermediate TBSRTC categories. Despite low diagnostic accuracy, considering its availability and low costs, NLR has merit for further studies.

Keywords: Goiter, Bethesda classification, fine needle aspiration biopsy, papillary thyroid carcinoma, thyroid nodule, neutrophil-to-lymphocyte ratio.

Introduction

During last decades, the incidence of thyroid cancer has been nearly tripled from 4.9 to 14.3 per 100,000 people in United States due to increasing diagnosis of thyroid nodules[1]. The major issue in evaluation of thyroid pathologies is distinguishing benign and malign nodules. Up to 15% of all clinically detected thyroid nodules are found to be malignant [2]. Ultrasonography and fine needle aspiration biopsy (FNAB) are the most common diagnostic tools with high specificity to detect thyroid cancer, however one-third of the cytologic evaluation cannot provide a certain diagnosis.

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In 2007, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has been introduced to standardize a category-based reporting system for thyroid FNAB including 6 categories, each indicating an implied cancer risk [3]. According to the 2017 update for TBSRTC system, 20-30% of the cases are reported as intermediate category with reported rates of cancer 10-30% for TBSRTC III, 25-40% for TBSRTC IV and 50-75% for TBSRTC V [3-5]. Several studies have validated the risk stratification of TBSRTC and the increase in diagnostic value of FNAB with the use of TBSRTC [6-9]. Particularly in intermediate categories, Bethesda system has limited diagnostic accuracy [7,10,11]. Repeating FNAB [3], lobectomy [3], sonographic risk stratification [5,10] and molecular tests [12] have been recommended for more accurate preoperative staging in TBSRTC III, IV and V categories, however these tools come with potential interventional complications and increased costs. These concerns lead to focus on more feasible additional tools to improve preoperative risk assessment [5,12].

The systemic inflammatory response is considered to promote different stages of cancer development and invasion. Several studies reported that elevated preoperative NLR is associated with deeper tumor invasion, advanced stage, and poor prognosis in different tumors [13-16]. The significance of NLR in detecting thyroid papillary microcarcinomas was first reported in 2013 [17]. After that many studies have suggested that NLR, as a marker of systemic inflammation, is related with tumor characteristics and prognosis in thyroid cancer [18-20]. Neutrophil-to-lymphocyte ratio may be an easily accessible and inexpensive tool for preoperative decision-making particularly in patients with conflicting preoperative FNAB results.

Aim of this study is to investigate the diagnostic accuracy of preoperative NLR for predicting cancer in TBSRTC III, IV and IV thyroid nodules.

Materials and Methods

The study was approved by institutional ethic committee (IRB: 10840098-604.01.01-E.45124). All the patients gave written consent for treatments and participating in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

An institutional board-approved database of thyroidectomy was reviewed. The data of the patients who underwent bilateral thyroidectomy for thyroid nodules between 2012 and 2018 were retrospectively analyzed. Bethesda classification has been put into practice in 2012 in our institution. Patients who had available laboratory tests, FNAB reports and TBSRTC classification were included in

the study. Neutrophil to lymphocyte ratio was calculated from routine preoperative laboratory tests. The impedance method (Beckman Coulter LH 750) was used for complete blood count. All the patients underwent FNAB and thyroidectomy at the same institution. American Thyroid Association (ATA) guidelines were followed in the management of thyroid nodules [21]. Biopsies were performed by radiologists under ultrasound guidance. None of the specimens were on-site evaluated for adequacy. Two experienced pathologists evaluated the specimens at institutional pathology laboratory. The cytologic evaluation was reported according to current TBSRTC classifications [3]. Patients who did not have preoperative complete blood count within 1 week before the surgery, FNAB reports which were not available or did not report Bethesda classification and patients who had signs of thyroiditis, immunosuppression; chemotherapy history or any infectious process within 2 weeks before the surgery were excluded from the analysis.

The primary endpoint of the study was assessing the diagnostic accuracy of preoperative NLR for detecting thyroid cancer in patients who had intermediate (TBSRTC III, IV and V) preoperative FNAB reports.

Statistical analysis

SPSS for Windows 21.0 (IBM, IL, USA) was used for statistics. Continuous variables were expressed as means and standard deviation and categorical variables as frequency and percentages. The equality of distribution of NLR between variables was tested by Bonferroni analysis. Association between NLR and categorical variables was tested by independent samples *t* test and One-way ANOVA. Pearson's correlation test was used for analyzing association between NLR and continuous variables. Receiver operative characteristic curves were used to calculate the diagnostic accuracy parameters of NLR. Statistical significance was defined as $p < 0.05$.

Results

Between 2012 and 2018, 220 patients underwent thyroidectomy for thyroid nodules in our institution. The reason for exclusion was lack of proper pathology reports in 33 patients, blood count in 19 patients, and informed consent in 12 patients. Ten patients had thyroiditis and were not included in the analysis. Totally 146 patients were included in the study. The mean age was 45.9 ± 13.6 , 109 (74.7%) patients were female and 37 (25.3%) were male. The mean NLR was 2.1 ± 1.1 . Postoperative pathologic examination revealed thyroid cancer in 92 (63%) of the patients. Details of the demographic and clinical characteristics, Bethesda system and postoperative pathology are given in table 1.

The TBSRTC classification was intermediate in 57 (39%) patients. The mean NLR in this subgroup was 2.1 ± 0.8 . The

mean NLR was similar between TBSRTC III, IV and IV groups ($p=0.737$) (Table 2). Thyroid cancer was detected in postoperative pathologic evaluation in 38 (66.7%) patients. The mean NLR was 2.4 ± 0.8 in thyroid cancers and significantly higher when compared with patients with benign postoperative pathology (1.6 ± 0.4 , $p=0.014$). There was a significant difference between papillary and follicular

cancer; the mean NLR was 2.3 ± 0.8 in papillary cancer and 2.6 ± 0.7 in follicular cancer patients ($p=0.005$). The cut-off value of NLR for predicting cancer at 89% sensitivity and 53% specificity was 1.6 (Area under curve [AUC]: 0.769, 95% confidence interval [CI]: 0.643-0.895, $p=0.001$) (Figure 1). The accuracy of NLR for different cut-off values is given in table 3.

Table 1. Demographic and clinical characteristics of the patients and the relationship with neutrophil-to-lymphocyte ratio.

	n=146	NLR (mean±SD)	p
Sex (n, %)			0.076*
Female	109 (74.7)	2.1±1.1	
Male	37 (25.3)	1.8±0.5	
Age (year, mean±SD)	45.9±13.6		0.795**
TSH (mIU/L, mean±SD)	5.58±21.4		0.385**
FNAB (n, %)			0.863***
TBSRTC I	3 (2.1)	1.8±0.8	
TBSRTC II	50 (34.2)	1.9±1.3	
TBSRTC III	15 (10.3)	2.2±0.8	
TBSRTC IV	13 (8.9)	1.9±0.9	
TBSRTC V	29 (19.9)	2±0.7	
TBSRTC VI	36 (24.7)	2.1±0.9	
Pathology (n, %)			0.026*
Benign	54 (37)	1.8±0.2	
Cancer	92 (63)	2.2±0.8	
Papillary cancer	87 (59.6)	2.2±0.8	0.096***
Follicular cancer	3 (2.1)	2.5±0.9	
Lymphoma	1 (0.7)	3.1	
Medullary cancer	1 (0.7)	2.4	
Tumor size (mm, mean±SD)	1.9±1.3		0.564**

NLR: neutrophil-to-lymphocyte ratio, FNAB: Fine needle aspiration biopsy, TBSRTC: The Bethesda System for Reporting Thyroid Cancer, *Independent samples *t* test, **Pearson correlation, ***One-way ANOVA

Table 2. Details of the patients with intermediate category fine needle aspiration pathology reports.

	n=57 (%)	NLR (mean±SD)	p
FNAB			0.737***
TBSRTC III	15 (26.3)	2.21±0.8	
TBSRTC IV	13 (22.8)	2±0.9	
TBSRTC V	29 (50.9)	2.1±0.7	
Pathology			0.014*
Benign	19 (33.3)	1.6±0.4	
Cancer	38 (66.7)	2.4±0.8	
Papillary cancer	36	2.3±0.8	
Follicular cancer	2	2.6±0.7	0.005***

NLR: neutrophil-to-lymphocyte ratio, FNAB: Fine needle aspiration biopsy, TBSRTC: The Bethesda System for Reporting Thyroid Cancer, ***One-way ANOVA, *Independent samples *t* test

Table 3. Diagnostic accuracy analysis for neutrophil-to-lymphocyte ratio

NLR	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV	Accuracy
1.4	95%	82.2-99.4	31%	12.6-56.6	74%	75%	74%
1.6	89%	75.2-97.1	53%	28.9-75.6	79%	71%	77%
1.8	63%	45.6-78.2	63%	38.4-83.7	77%	46%	63%
2.1	55%	38.3-71.4	90%	66.9-98.7	91%	50%	67%
2.5	29%	15.5-45.9	95%	73.9-99.9	92%	40%	51%

Discussion

The Bethesda classification alone may fail in preoperative decision making in intermediate risk category thyroid biopsies [11]. Different complimentary adjunct diagnostic tools including molecular testing and imaging modalities have been suggested to enhance the confidence of preoperative diagnosis. However, there are limited and conflicting data regarding the relationship between preoperative inflammatory biomarkers and thyroid cancer. We found increased preoperative NLR values in patients who were preoperatively in intermediate stages of Bethesda but diagnosed with cancer after surgery. This increase was more remarkable in follicular cancer. Our results showed that preoperative elevated NLR was associated with higher risk of thyroid cancer in intermediate TBSRTC categories.

Elevated preoperative NLR has been shown to be related with incomplete response to therapy [22], poor tumor differentiation [23], lymph node invasion [24], advanced stage [25] and higher thyroglobulin values [26] in thyroid malignancies. On the other hand, in 2016, a meta-analysis of 6 prospective cohorts with 6283 differentiated thyroid cancer patients revealed no difference in NLR between patients with cancer and benign nodules with a mean difference of 0.19 (95% CI: -0.09-0.46, $p < 0.001$). This meta-analysis concluded that an elevated NLR could not predict differentiated thyroid cancer, however well-designed large studies were needed [27].

In 2017, Manatakis et al [28] reported poor clinicopathological characteristics including extrathyroidal invasion ($p=0.04$), bilateral ($p=0.03$) and multifocal tumors ($p=0.01$) and lymph node metastasis ($P=0.03$) in thyroid papillary cancer patients with higher NLR. The NLR value was not influenced by sex, age, tumor size or cytology in this study. Conformably with these findings, NLR was not associated with age ($p=0.795$), sex ($p=0.076$), TSH (0.385), FNAB results ($p=0.863$) and histologic subtype ($p=0.096$) in our total series, however in subgroup analysis of intermediate TBSRTC categories NLR was significantly higher in follicular cancer ($p=0.005$). The diagnostic accuracy of systemic inflammatory markers have been evaluated in a recent study including 397 patients by the same group [29]. They found significantly higher NLR ($p=0.026$) in carcinomas and

microcarcinomas compared to benign nodules, but similar platelet-to-lymphocyte ratio values between cancer and benign pathology. The diagnostic accuracy of NLR was 45-50% in their study. In our study accuracy ranging between 51 to 74% was higher than previous studies but still unsatisfying. Our analysis focused on the presence of cancer in intermediate Bethesda stages, therefore we did not assess the relationship between NLR and prognostic clinicopathologic factors. Other major drawback of our study is limited number of cases.

Conclusion

The recent guideline of ATA [21] recommends that molecular tests and radiology can be used to support cytology in cases with indeterminate FNAB, pointing out that the positive and negative predictive values of all diagnostic tools are influenced by the individual cancer rate in each cytologic category, which varies widely at different institutions [12]. There is no doubt that none of the diagnostic tolls alone can provide a certain recommendation of follow-up or surgery. Patients in this ‘gray zone’ should be evaluated individually with all cytologic and radiologic findings to determine the cancer risk. Despite limited and conflicting evidence in the literature, preoperative NLR is an internationally available, fast and easy measurement which can be suggestive when discussing the management, thus should be kept noteworthy for further studies.

Conflicts of interest

Authors declare no potential conflict of interests. The study received no funding.

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