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The neutrophil to lymphocyte ratio can discriminate anaplastic thyroid cancer against poorly or well differentiated cancer

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Purpose: We evaluated the capability of the neutrophil to lymphocyte ratio (NLR) as a diagnostic tool to discriminate between poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) from well differentiated thyroid cancer (WDTC).
Methods: The NLR of 3,870 patients with benign and malignant thyroid tumors were analyzed. There were 436 benign, 3,364 papillary, 15 medullary, 34 follicular or hurthle type, 14 PDTC, and 7 ATC type neoplasms. Patients were divided into two groups: a high NLR group and a low NLR group.
Results: The NLR of all 3,870 patients was a normal distribution, and the median value was 1.57. Advanced stage cancer, such as T3 or T4 was high (30.4% *vs.* 26.5%, P = 0.027), and cancer-specific deaths were also high (1.2% *vs.* 0.4%, P = 0.018) in the high NLR group. The proportion of PDTC (0.6% *vs.* 0.1%) and ATC (0.3% *vs.* 0.1%) was higher in the high NLR group. The NLR can discriminate between PTC, PDTC, and ATC (P = 0.035, P = 0.002, and P = 0.025, respectively), and the cutoff value was 3.8 between PDTC versus ATC. None of the NLR of PDTC exceeded the cutoff value of 3.8.
Conclusion: NLR can play a relevant role as a discriminating tool and may be considered as a new diagnostic criterion in discriminating as well as in selecting therapeutic approaches to these aggressive forms of thyroid cancer.
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Key Words: Neutrophils, Lymphocytes, Thyroid neoplasms, Inflammation

INTRODUCTION

The World Health Organization (WHO) Classification of Tumors in 2004 defined poorly differentiated thyroid cancer (PDTC) as "follicular-cell neoplasms that show limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviorally an intermediate position between well differentiated thyroid cancer (WDTC) and anaplastic thyroid cancer (ATC)" [1-4]. The occurrence of a mutation in the *p53* gene is considered a key event in the malignant progression of WDTCs toward the development of highly aggressive undifferentiated tumors. In both PDTCs and ATCs, prognosis is negatively affected by *p53* mutations, which contribute actively to tumor maintenance, spreading, and increased resistance to conventional anticancer treatments [5,6]. To date, most of the work has focused on the histological and immunohistochemical markers. These markers, while effective, are often expensive and time-consuming to use.

Inflammatory status can lead to enhance tumor growth, invasion, angiogenesis, and eventually metastasis [7-9]. Tumor-host interactions may have significant influences on patients' outcomes, but this effect is rarely taken into account in current

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diagnostic or prognostic systems. There is now accumulating evidence that the markers of the systemic inflammatory response, including cytokines, CRP, albumin, serum amyloid A, and WBC count are able to contribute as prognostic factors in cancer patients [10-12]. Neutrophil to lymphocyte ratio (NLR) is a simple index of the systemic inflammatory response, and has been shown to be a prognostic indicator in some types of cancer.

Thyroid cancer commonly shows a close association with inflammation. Several articles have shown that there is an increased incidence of differentiated thyroid cancer in patients with thyroiditis [13,14]. High preoperative NLR has been associated with increased tumor size and high American Thyroid Association (ATA) risk of recurrence in patients with differentiated thyroid cancer [15]. Additionally, the intratumoral lymphocyte and immature dendritic cell infiltrate is reduced or absent in PDTC and ATC [16]. NLR is cheaper than serum CRP, which is now routinely measured as part of the cancer work-up, easily calculated, and universally available. We hypothesized that the NLR could be used as an effective discriminating tool in these subtypes of thyroid cancer.

METHODS

Patients who underwent thyroid surgery in Gwangju and Hwasun Chonnam National University Hospitals between January 2004 and March 2009 were identified from a prospectively maintained database. The database is prospectively maintained and all patients are followed-up regularly by a team of thyroid cancer specialists. In total, 3,870 patients were enrolled, including some patients who did not undergo any surgical procedures but had a definite diagnosis on cytological examination.

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. For patients who underwent surgery, the NLR was calculated from the full blood count routinely performed on the 7th–14th day before surgery. For patients who did not undergo surgery, the NLR was calculated from the full blood count performed as part of the diagnostic process. The median NLR of all 3,870 patients was 1.57, and evenly divided into 1,935 patients on each groups: the neutrophilic high NLR group and the lymphophilic low NLR group. The preoperative and postoperative profiles were analyzed.

Patients were excluded from the study for the following reasons: not enough data on follow-up, pediatric patients, patients with other cancer history or distant metastasis, and previous history of infectious conditions such as pulmonary or visceral tuberculosis.

Data were summarized with the number of subjects and the mean ± standard deviation or median (range) value. We used the t-test to compare continuous variables between each group and the chi-square test for categorical variables. Mann-Whitney U test was used to compare categorical end points and the two-sample t-test was used to compare continuous variables. A receiver operating characteristics curve was constructed to estimate the optimal cutoff value of pretreatment NLR and other variables. Subsequently, the variables with $P < 0.05$ entered into the multivariate analysis. Statistical significance was indicated by a P-value of <0.05. Results were analyzed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Demographics

The NLR of all 3,870 patients was a normal distribution with a median value of 1.57 (0.28–16.29). We assumed the higher NLRs to be an indicator of an aggressive tumor type, advanced TNM stage, and poor prognostic factors. We divided the patients into two groups: the neutrophilic high NLR group and the lymphophilic low NLR group. Table 1 shows the demographics of enrolled patients and their respective preoperative and postoperative profiles. age, sex, tumor type or size, N stage, and initial distant metastases were not significantly different. There were no difference in the proportion of patients with hypertension (16.5% *vs.* 16.6%, $P = 0.970$) and diabetes (6.5% *vs.* 5.4%, $P = 0.134$), and the chance or dose of radioactive iodine ablation and recurrences were not different between the two groups.

Correlation with advanced stage

Advanced T stage, above T3 or T4, cancer-specific death, and the proportion of PDTC and ATC were higher in the high NLR group. We excluded 436 benign tumors and analyzed the remaining 3,434 malignant cancers. There was no difference in N stage ($P = 0.083$), and M stage ($P = 0.367$), but advanced stages, such as T3 or T4, were significantly more distributed on high NLR groups rather than low NLR groups (30.4% *vs.* 26.5%, respectively, $P = 0.027$). Cancer-specific death (1.2% [high NLR] *vs.* 0.4% [low NLR], $P = 0.018$), and the proportion of PDTC and ATC (0.9% [high NLR] *vs.* 0.2% [low NLR], $P = 0.022$) were higher in the high NLR group. In subanalysis on WDTC, tumor size was not different (0.85 cm [high NLR] *vs.* 0.9 cm [low NLR, $P = 0.141$), and there were no differences in cancer-specific death (0.5% [high NLR] *vs.* 0% [low NLR], $P = 0.066$; data not shown).

Correlation with prognosis

Cancer specific death was also high (1.2% [high NLR] *vs.* 0.4% [low NLR], $P = 0.018$) in high NLR groups, and 21 cancer-specific deaths (0.8%) occurred. Of the 21 deaths, six were with WDTC, 10 out of 14 were PDTC, and 5 out of 7 were ATC.

Anaplastic transformation in PD carcinoma is not infrequent, and its prognosis is greatly affected even when the foci of dedifferentiation are small [17]. Of the 10 PDTC deaths, progression to ATC also occurred in seven patients, and the other three patients died due to the progression of PDTC. The initial ATC patients (5/7) also died of these cancers.

Role of benign tumor discrimination

Table 1 shows the distribution of various tumor types, including benign or malignant tumors, between two groups. We

Table 1. Demographics and characteristics of all tumor types according to NLR ratio

Variable	All patients (n = 3,870)	High NLR all (n = 1,935)	Low NLR all (n = 1,935)	P-value
Age (yr)	47.0 ± 12.1	46.9 ± 12.0	47.2 ± 12.2	0.399
>45	2,227 (57.5)	1,098 (56.7)	1,129 (58.3)	0.329
Male sex	641 (16.6)	318 (16.4)	323 (16.7)	0.829
Tumor size (cm)	0.9 (0.1–10.2)	0.9 (0.1–10.2)	0.85 (0.1–8.5)	0.141
NLR	1.57 (0.28–16.29)	2.13 (1.57–16.29)	1.21 (0.28–1.57)	<0.001
WBC count	6,240 ± 1,766	6,797 ± 1,893	5,683 ± 1,425	<0.001
Neutrophil (%)	55.6 ± 10.0	63.3 ± 7.1	47.8 ± 5.6	<0.001
Lymphocyte (%)	34.5 ± 9.1	27.4 ± 6.1	41.6 ± 5.3	<0.001
Tumor type				
Benign NH, TFA	436 (11.3)	210 (10.9)	226 (11.7)	0.416
PTC	3,364 (86.9)	1,679 (86.8)	1,685 (87.1)	0.775
MTC	15 (0.4)	10 (0.5)	5 (0.3)	0.196
TFC HCC	34 (0.9)	18 (0.9)	16 (0.8)	0.730
PDTC	14 (0.4)	12 (0.6)	2 (0.1)	0.013
ATC	7 (0.2)	6 (0.3)	1 (0.1)	0.070
T stage				0.027
T0	436 (11.3)	210 (10.9)	226 (11.7)	
T1T2	2,333 (60.3)	1,137 (58.8)	1,196 (61.8)	
T3T4	1,101 (28.4)	588 (30.4)	513 (26.5)	
N stage				0.083
N1a	660 (17.1)	326 (16.8)	334 (17.3)	
N1b	223 (5.8)	106 (5.5)	117 (6.0)	
M1 stage	31 (0.8)	18 (0.9)	13 (0.7)	0.367
Radioactive iodine therapy	1,106 (28.6)	513 (26.5)	593 (30.6)	0.107
RAI cumulative dose (mCi)	150 (30–1,350)	150 (30–1,350)	150 (30–1,310)	0.723
Recurrence	209 (5.4)	108 (5.6)	101 (5.2)	0.619
Thyroid cancer death	21 (0.8)	16 (1.2)	5 (0.4)	0.018

Values are presented as mean ± standard deviation, number (%) or median (range).
NLR, neutrophil-lymphocyte ratio; NH, nodular hyperplasia; TFA, thyroid follicular adenoma; PTC, papillary thyroid cancer; MTC, medullary thyroid cancer; TFC, thyroid follicular cancer; HCC, Hurthle cell carcinoma; PDTC, poorly differentiated cancer; ATC, anaplastic cancer; RAI, radioactive iodine therapy.

Table 2. Discrimination of tumor types

Type	Proportion	NLR	NLR	PTC	MTC	TFC HCC	PDTC	ATC
NH TFA	436 (11.3)	1.95 ± 1.33	1.55 (0.47–13.83)	0.739	0.241	0.886	0.055	0.003
PTC	3,364 (86.9)	1.86 ± 1.16	1.57 (0.28–16.29)	1	0.178	0.750	0.035	0.002
MTC	15 (0.4)	2.00 ± 0.82	1.80 (0.98–3.90)		1	0.362	0.621	0.026
TFC HCC	34 (0.9)	1.86 ± 0.91	1.60 (0.66–3.79)			1	0.173	0.007
PDTC	14 (0.4)	2.13 ± 0.76	1.87 (1.17–3.71)				1	0.025
ATC	7 (0.2)	5.51 ± 4.45	3.81 (1.19–14.07)					1

Values are presented as number (%), mean ± standard deviation or median (range).
All statistics calculated via the Mann-Whitney U test.
NLR, neutrophil-lymphocyte ratio; PTC, papillary thyroid cancer; MTC, medullary thyroid cancer; TFC, thyroid follicular cancer; HCC, Hurthle cell carcinoma; PDTC, poorly differentiated cancer; ATC, anaplastic cancer; NH, nodular hyperplasia; TFA, thyroid follicular adenoma.

found that the 436 benign tumors, such as nodular hyperplasia (NH) or follicular adenoma, were not different while the 3,364 papillary, 15 medullary, and 34 follicular or hurthle type cancers were also not significantly different in NLR distribution in each type of cancers.

Further analysis with Mann-Whitney U test shows the discriminating role of NLR according to tumor type (Table 2). NLR cannot discriminate between benign NH and thyroid follicular adenoma (TFA) and malignant tumors, and cannot discriminate TFA from thyroid follicular carcinoma (P = 0.886).

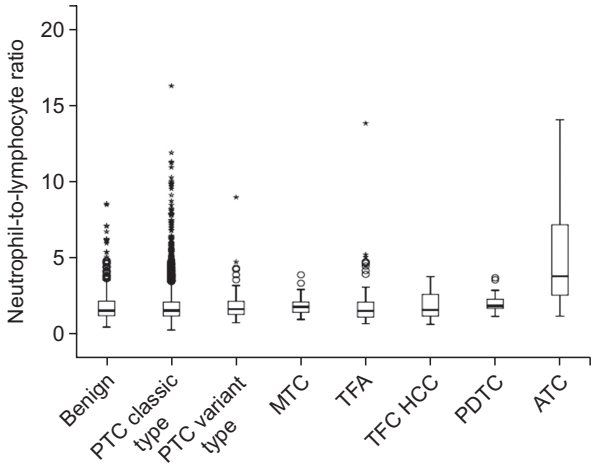

Fig. 1. Neutrophil-lymphocyte ratio can discriminate anaplastic thyroid carcinoma from other types of thyroid cancer, especially poorly differentiated thyroid carcinoma (P = 0.025). The cutoff value was 3.8. PTC, papillary thyroid cancer; MTC, medullary thyroid cancer; TFA, thyroid follicular adenoma; TFC, thyroid follicular cancer; HCC, Hurthle cell carcinoma; PDTC, poorly differentiated cancer; ATC, anaplastic cancer.

Discrimination of PDTC or ATC from PTC

There were 14 PDTC, seven ATC, and 3,364 patients with PTC. Of the 21 patients, 85.7% of both tumor types (18/21) had a high NLR equal to or above 1.57. The proportion of PDTC (0.6% [high NLR] *vs.* 0.1% [low NLR]) and ATC (0.3% [high NLR] *vs.* 0.1% [low NLR]) was significantly higher in the high NLR group (Table 1). The NLRs of PDTC and ATC were significantly higher and were able to discriminate PDTC from PTC (P = 0.035), ATC from PTC (P = 0.003), and ATC from PDTC (P = 0.025) (Table 2). The cutoff value for discriminating PDTC from ATC was 3.8 (Fig. 1), and none of the NLRs of ATC fell below the cutoff value of 3.8 (Table 3).

DISCUSSION

The process of the development of malignancy has been firmly associated with impaired function of the immune system [18]. Recently, many research centers have begun examining the host's inflammatory response to tumors and the systemic effects exerted by tumors in causing up-regulation of the inflammatory process, and thus increasing the propensity of metastasis through the inhibition of apoptosis, promotion of angiogenesis, and DNA damage [7,19-21]. Prior studies have demonstrated an association between simple inflammatory markers (blood neutrophil, lymphocyte, and platelet counts) and adverse effects in certain types of cancer (stomach, colon, bladder, esophageal, pulmonary, ovarian, pancreas, renal and others). Representatively, Bruckner et al. [22] found that pretreatment absolute neutrophil and lymphocyte count were

Table 3. Characteristics of poorly differentiated and anaplastic carcinoma

Characteristic	PDTC (n = 14)	ATC (n = 7)	P-value
NLR	1.87 (1.17–3.71)	3.81 (1.19–14.07)	0.001
WBC count	7,000 ± 1,797	9,457 ± 3,432	0.115
Neutrophil (%)	59.4 ± 7.5	70.5 ± 13.3	0.115
Lymphocyte (%)	29.7 ± 7.0	19.6 ± 11.4	0.184
Age (yr)	50.0 ± 11.1	64.9 ± 17.0	0.161
>45	10 (71.4)	6 (85.7)	0.624
Male sex	9 (64.3)	3 (42.9)	0.397
Tumor size (cm)	3.4 (1.2–7.0)	6.4 (0.5–10.0)	0.231
Distant metastasis	3 (21.4)	1 (14.3)	1.000
RAI	10 (71.4)	1 (14.3)	0.044
RAI cumulative dose (mCi)	350 (150–400)	350	<0.001
External radiotherapy	7 (50.0)	5 (71.4)	0.642
Chemotherapy	2 (14.2)	0 (0)	0.575
Recurrence	11 (78.6)	2 (28.6)	0.056
Thyroid cancer death	10 (71.4)	5 (71.4)	0.741

Values are presented as median (range), mean ± standard deviation or number (%).
PDTC, poorly differentiated cancer; ATC, anaplastic cancer; NLR, neutrophil-lymphocyte ratio; RAI, radioactive iodine therapy.

independent prognostic indicators for patients with metastatic gastric cancer. Later, the NLR was observed to be significantly elevated in the advanced stages of colorectal cancer [23].

In our study, advanced stage of the disease, such as T3 or T4, cancer-specific death, and the proportion of PDTC to ATC was significantly more distributed in the high NLR group. Some studies have shown that high preoperative NLR is associated with an increased tumor size and high ATA risk of recurrence in patients with differentiated thyroid cancer [15]. Unfortunately, in our study, tumor size and cancer-specific deaths in the subanalysis of WDTC with NLR were not different, and we did not discriminate between malignant cancers and benign tumors. However, the proportion of PDTC and ATC was significantly higher in the high NLR group. The NLR was the only diagnostic tool for discriminating between WDTC, PDTC and ATC.

PDTC lies both morphologically and behaviorally between WDTC and undifferentiated ATC [4,17,24]. PDTC and ATC have poor prognoses and rare incidence rates compared to WDTC. Since the original description of PDTC in 1983 [25], PDTC has been introduced as a separate entity in the 2004 WHO Classification of endocrine tumors [1]. From a histopathogenetic point of view, as for undifferentiated (anaplastic) carcinomas, it is generally accepted that PDTC may arise de novo or from preexisting well differentiated follicular and papillary carcinomas. However, definite molecular (and prevalence) data are difficult to obtain from the published literature, which reflect confusing terminology and the heterogeneous classification criteria debated above [17].

ATC is a rare but aggressive form of cancer that accounts for <2% of all thyroid malignancies [26]. The results of surgical resection, chemotherapy and radiotherapy, alone or in combination, are not effective and patients usually die within 6–12 months [27,28]. This clinical behavior and outcome is dramatically different from that observed in WDTCs, which usually grow and progress slowly, rarely metastasize, and are characterized by a good or very good prognosis. Our series have shown that ATC have a distinct NLR from that of PDTC and WDTC. Therefore, we constructed a simple approach in an effort to streamline the diagnosis of ATC versus PDTC and WDTC with NLR.

The processing of discrimination between PDTC and ATC is very difficult even with microscopic examination and immunohistochemical staining and clinical outcome data. In our patients between 2004 and 2009, 14 patients had PDTC and seven had completely discriminated ATC. Two pathologists from different institutions reviewed and confirmed the diagnoses of 21 patients with PDTC or ATC. Although there is much limitations remains to be done. The incidences of PDTC and ATC are very low, so too small numbers were enrolled in this study. But our work generates important findings in the field of distribution of NLR. Importantly, the NLR was also a meaningful diagnostic tool for discriminating PDTC and ATC. The NLR can discriminate between PTC, PDTC, and ATC ($P = 0.035$, $P = 0.002$, and $P = 0.025$, respectively), with a cutoff value of 3.8. The use and validation of uniform internationally accepted criteria for PDTC and ATC should be encouraged to garner a better understanding of their pathogenetic origin, to search for potentially helpful diagnostic, prognostic, and predictive markers, to plan therapy, and to establish the epidemiologic distribution of these tumor entities.

In conclusion, we demonstrated that the NLR is significantly different and high in PDTC and ATC as compared to WDTC, and represents a poor prognosis for those cancers. Therefore, NLR can play a relevant role as a discriminating tool and may be considered as a new diagnostic criterion in discriminating these aggressive forms of thyroid cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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