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

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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 clinical practice.

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.

Key Words: Neutrophils, Lymphocytes, Thyroid neoplasms, Inflammation
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 group: 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) | 0.9 (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) | 0.397 |
| T1T2 | 2,333 (60.3) | 1,137 (58.8) | 1,196 (61.8) | 0.991 |
| T3T4 | 1,101 (28.4) | 588 (30.4) | 513 (26.5) | 0.168 |
| N stage |  |  |  | 0.083 |
| N1a | 660 (17.1) | 326 (16.8) | 334 (17.3) | 0.298 |
| N1b | 223 (5.8) | 106 (5.5) | 117 (6.0) | 0.086 |
| M1 stage | 31 (0.8) | 18 (0.9) | 13 (0.7) | 0.007 |
| 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 (0.5) | 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).

**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

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**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 (5.5–10.0) | 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.
in our study, tumor size and cancer-specific deaths in the suba-

patients with differentiated thyroid cancer [15]. Unfortunately,
with an increased tumor size and high ATA risk of recurrence in
studies have shown that high preoperative NLR is associated
significantly more distributed in the high NLR group. Some
cancer-specific death, and the proportion of PDTC to ATC was
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
tumor size and cancer-specific deaths in the suba-

analysis 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 sur-
gical 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 immu-
nohistochemical 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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