Original Article

Association of Neutrophil-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio with Clinicopathological Features and Short-Term Outcome in Well-Differentiated Thyroid Cancer

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Abstract

Purpose of the Study: To assess the association of inflammatory markers with known risk factors and short-term outcome of well-differentiated thyroid cancer. **Materials and Methods:** Well-differentiated nonmetastatic thyroid cancer patients diagnosed and treated between September 2015 and December 2019 at Kasturba Hospital, Manipal, India, were retrieved for the study. Patients' presurgical blood parameters were noted, and neurtrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) were calculated. Clinicopathological details along with tumor markers at baseline and at 6 months' follow-up were tabulated. Patients were categorized as complete disease clearance if their clinical examination was normal, stimulated thyroglobulin (Tg) was <1 ng/ml, Anti-thyroglobulin antibodies <65 IU/L or showing a decreasing trend, and follow-up I-131 whole-body scan was negative. The association of the inflammatory markers with known risk factors and short-term outcomes were compared. **Results:** A total of 272 patients were analyzed in the study. The median NLR in our study cohort was 2.55 (mean = 3.96 with standard deviation [SD] =4.20) and the median LMR was 3.72 (mean = 3.79 with SD = 1.94). The disease clearance rate of our study cohort was 73.9%. The median NLR (2.4 vs. 3.1) and LMR (3.13 vs. 3.93) were significantly different among the patients with complete disease clearance and those with persistent disease ($P = 0.008$ and $P = 0.003$, respectively). The known risk factors such as multifocality ($P = 0.04$), tumor size ($P = 0.013$), lymph node metastases ($P = 0.001$), and baseline Tg ($P \leq 0.001$) were significantly associated with persistent disease at 6 months. The NLR showed a positive correlation and LMR had a negative correlation with the known risk factors, however, the associations were not statistically significant. **Conclusions:** The NLR and LMR are simple yet potential prognostic tools in well-differentiated thyroid cancer.

Keywords: *Inflammatory markers, lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, well-differentiated thyroid cancer*

Introduction

The malignant diseases of the thyroid account for around 3% of all cancers in human.[1] As per the GLOBOCON 2020 estimates, it is one of the top 10 cancers globally, with more than half a million new cases being diagnosed annually.[1] Histologically, well-differentiated thyroid carcinoma (DTC), in the form of papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma, account for more than 90% of thyroid malignancies, contrasting the undifferentiated or poorly differentiated tumors such as anaplastic cancer and medullary thyroid cancer that amount to a minority of cases.[2] Majority of the DTC have a peculiar clinic-pathological behavior and exhibit excellent therapeutic responsiveness, while around 6%–20% of DTC patients tend to manifest aggressive disease and fare poorly.[3] Age >55 years, tumors of size >4 cm, presence of metastatic cervical lymphadenopathy, gross extrathyroidal extension, and distant metastasis are some of the well-known predictors of the aggressive and poorly-responding DTC.[2] Consequently, DTC without any of these features are considered as low-risk tumors. This has led to a paradigm shift toward de-intensification of therapeutic approaches for DTC that are at low risk of recurrence. However, a proportion of these low-risk DTC can also exhibit poor therapeutic response and consequently exhibit unfavorable prognosis. Currently, there are no reliable clinical predictors to predict the therapeutic responsiveness

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amongst the low- and intermediate-risk DTC. In this regard, although molecular markers such as BRAF V600E mutation, could suggest an aggressive disease irrespective of the clinical risk stratification, the limited availability of the molecular diagnostics render them ineffective for clinical use, particularly in emerging nations.[4,5] In the quest of a reliable and feasible determinant of prognosis, some of the researchers have evaluated peripheral blood cell ratios, such as neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR).[6-8] Interestingly, some of the recent studies have reported these inflammatory markers, to be consistent and reliable, for predicting the aggressive and high-risk DTC.[8-13] However, it remains to be seen if the inflammatory markers such as NLR and LMR can be of any prognostic value even when the clinically high-risk determinants (such as large primary tumors with gross extrathyroidal extension and distant metastasis) are taken out of the equation, as these factors are anyway known to harbor relatively poorer outcomes. In other words, the predictive ability of NLR and LMR in a homogenous cohort of low and intermediate-risk DTC is yet to be determined. In view of these observations, we undertook the present study, with an aim of evaluating the association of NLR and LMR with the therapeutic responsiveness, in patients with low and intermediate-risk DTC. The secondary objective is to evaluate the association of these ratios with the known predictors of prognosis in the same group of patients.

Materials and Methods

Study setting

This retrospective observational study was conducted at a tertiary care center, by the department of nuclear medicine. All the adult patients (aged 18 years and above) with histologically proven DTC, who had been operated and received radioiodine ablation at our center between January 2015 and December 2019 were considered for possible inclusion. Those with any type of thyroid surgery that is less than the total thyroidectomy, who did not receive a radioiodine scan at our center, and whose medical records were missing or lost to follow-up were automatically excluded from the study cohort. Patients having distant metastases, those with chronic inflammatory conditions, such as autoimmune diseases, asthma, atopy, and inflammatory bowel diseases were also excluded. Furthermore, as the Hashimoto`s thyroiditis is known to alter the NLR ratio, we excluded DTC with Hashimoto`s thyroiditis from the final analysis.[14] Similarly, those with the immunosuppression, either primary or secondary, and those with previous known malignancies were not considered for analysis. Finally, we also excluded locally infiltrative tumors/gross extrathyroidal extension (T4) and metastatic lesions from the analysis, as they have already shown to have a strong correlation with NLR, and our objective in this study is to evaluate the predictive ability of NLR in low- and intermediate-risk DTC.[7,8,15]

Data collection and segregation

The medical records of eligible patients were reviewed for the demographic details (age, gender, smoking status, and comorbidities), pathological characteristics of tumor (histological type, multifocality, size of the largest primary lesion, nodal status, and microscopic extrathyroidal extension), presurgical biochemical parameters (total and differential white blood cell counts) and baseline tumor markers (stimulated thyroglobulin [Tg] and anti-Tg antibody levels [ATA]). The treatment-related factors (type of surgery, dose of radioiodine therapy), and status of the disease clearance after a minimum follow-up of 6 months' posttreatment were also recorded for each of the included patients. As for the radioiodine ablation is concerned, all our patients had received a dose of 30 mCi for the residual disease and 50 mCi for lymph node metastases.

For categorizing the status of disease clearance at follow-up, we used the standard guidelines endorsed by the professional bodies.[2,16] For each patient, to be declared as completely cleared of the disease during the follow-up, he/she should not have demonstrated any nodule on clinical examination or ultrasound, the stimulated Tg levels should be <1 ng/mL, ATA assay should be <65 or in decreasing trend, and the radioiodine (I-131) whole body scan should not show any evidence of abnormal uptake. Any deviations from these criteria led to the classification of the therapeutic outcome in such patient as having incomplete clearance. Finally, using the Microsoft Excel worksheet (@Microsoft Corporation Ltd), the NLR and LMR were tabulated for each patient separately.

Outcome analysis

The association between the calculated NLR and LMR and the status of disease clearance at the follow-up were evaluated statistically. Secondarily, the association between these ratios against the known prognostic factors of DTC, such as histopathology, focality, size of the largest primary lesion, nodal status, and extrathyroidal extension, were also assessed as secondary outcome. We evaluated the ratios and therapeutic outcomes as per the histological types, by separating a group of PCT with high-risk variants such as tall cell, columnar cell, and diffuse sclerosing types.[17-19]

Statistical analysis

The analysis was performed using SPSS–23 (SPSS Statistics for Windows, Version 23; IBM SPSS Inc., Chicago, Illinois, United States) and the level of significance was fixed at 5%. Collected data was summarised by frequency, percentage, mean, standard deviation (SD), median, and interquartile range. Tests such as Chi-square test and Fisher's exact test were done to look for an association of known determinants such as tumor size, extrathyroidal extension, nodal status, high-risk histopathological variants, and stimulated Tg levels with the outcome at 6 months. Kruskal–Wallis and Mann–Whitney tests were performed to assess the association

between NLR and LMR with the above-mentioned known prognostic factors. Mann–Whitney test was done to assess the association between NLR and LMR with the outcome. The receiver operating characteristic curve was used to find the best cutoff NLR and LMR, with appropriate sensitivity and specificity.

Ethical approval

The study was approved by the institutional ethical committee (No. IEC1-335).

Results

A total of 1032 well-differentiated thyroid cancers were considered for the possible recruitment. Of these, about 102 patients, who presented with distant metastases or were diagnosed to have the M1 disease during post-surgical I-131 whole-body scan/F-18 FDG PET/CT were excluded from the study. The other excluded patients had final histopathology other than the well-differentiated malignancy (n = 134), chronic inflammatory conditions or previous malignancy (n = 152), lost to follow-up (n = 98), and missing clinical data (n = 274). A total of 272 patients were included in the final analysis, whose clinic-demographic details are summarised in Table 1. More than 80% of the study cohort were aged above 55 years and around 69% of the included patients were females. Pathologically, majority of the patients had T2 (49.3%) and N0 disease (54.8%). Papillary carcinoma was the most common histology (76.1%). Around 36.4% of our patients had a multifocal disease, and 27.6% had histologically extrathyroidal extension. Among the pathological lymph node positive cases (n = 123), 36.6% had the metastatic disease only in the central compartment (level VI), and the remaining had involved a lateral group of cervical lymph nodes (levels I-V) with or without level VI.

The median NLR in our study cohort was 2.55 (mean = 3.96 with [SD] =4.20) and the median LMR was 3.72 (mean = 3.79 with SD = 1.94). As for the outcome of therapy at follow-up, a total of 71 patients did not fulfill the criteria for disease clearance and hence were included under the group of incomplete or partial response. Statistical analyses of our study cohort demonstrated significant differences in the median NLR between the patients with complete response (2.40) and those with incomplete response (3.05) [Table 2]. By the ROC curve, the optimal cutoff NLR was 2.40 (sensitivity = 66.2%, specificity = 51.2%) [Figure 1]. Similarly, the median LMR also differed significantly between these groups (3.93 vs. 3.13), and the cutoff LMR with predictive ability was 3.93 (sensitivity = 67.6%, specificity = 50%) [Figure 2].

On analyzing the association of therapeutic outcomes with the other prognostic factors [Table 3], it was found that the high-risk pathological variants, advanced T stage, advanced N stage, multifocality, and elevated baseline Tg were significantly associated with incomplete therapeutic response. Although the NLR did not demonstrate any statistically significant associations with these predictors in our study, there was an appreciable trend of association between the elevated NLR with the multifocal disease, nodal positivity, extrathyroidal extension, and even with elevated levels of stimulated-Tg [Table 4].

Table 1: Characteristics of the 272 patients included in the study

Factor	Variables	*n* (%)
Age	<55	218 (80.15)
	>55	54 (19.85)
Sex	Female	188 (69.1)
	Male	84 (30.9)
Extent of surgery	Total thyroidectomy	169 (62.1)
	Total thyroidectomy + central neck dissection	35 (12.9)
	Total thyroidectomy + lateral neck dissection	68 (25)
Histopathology	Papillary carcinoma thyroid	207 (76.1)
	Follicular carcinoma thyroid	21 (7.7)
	High-risk variants of papillary carcinoma	44 (16.2)
Tumor-stage	1a	35 (12.9)
	1b	52 (19.1)
	2	134 (49.3)
	3	51 (18.8)
Nodal status	0	149 (54.8)
	1a	45 (16.5)
	1b	78 (28.7)
Extrathyroidal extension	Negative	197 (72.4)
	Positive	75 (27.6)
Focality	Unifocal	173 (63.6)
	Multifocal	99 (36.4)
Status at 6 months	Complete response	201 (73.9)
	Incomplete response	71 (26.1)

Table 2: Association between the ratios and outcomes/ therapeutic response at 6 months

Ratio	Outcome (response)	*n*	Median	IQR		*P* (Mann–Whitney test)
				Lower	Upper	
NLR	Incomplete	71	3.05	2.07	4.62	0.008
	Complete	201	2.40	1.73	3.58	
LMR	Incomplete	71	3.13	2.08	4.48	0.003
	Complete	201	3.93	2.74	4.89	

IQR: Interquartile range; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio

Discussion

As per the present consensus, the risk stratification in DTC is a dynamic process, in which the initial estimates of the risk of recurrence and disease-specific mortality need to be continuously re-evaluated over the time, at various stages through the treatment completion and surveillance, and must be modified as and when new information is available.[2] Currently, some of the clinicopathological

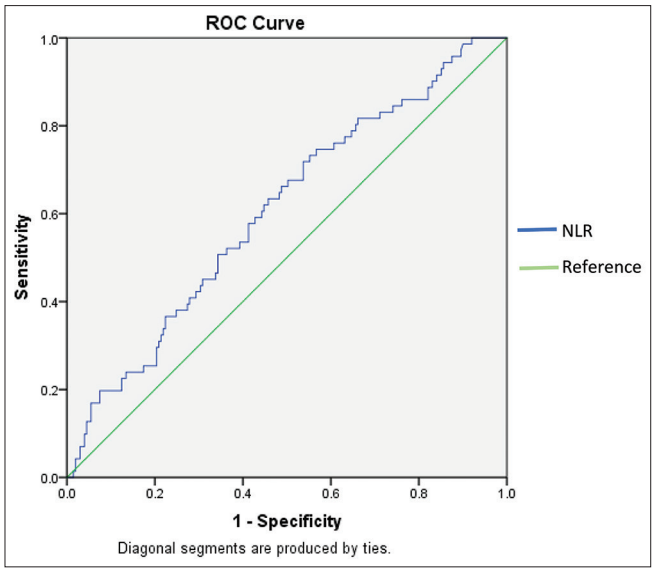

Figure 1: ROC curve for prediction of treatment outcome based on NLR. NLR: Neutrophil-to-lymphocyte ratio ; ROC: Receiver operating characteristic

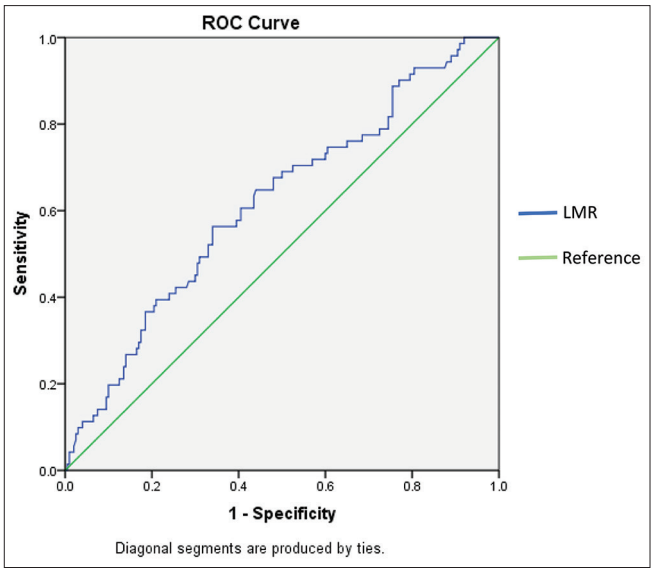

Figure 2: ROC curve for prediction of treatment outcome based on LMR. LMR: Lymphocyte- to-monocyte ratio ; ROC: Receiver operating characteristic

Table 3: Analysis of known risk factors with therapeutic outcomes at 6 months

	Disease clearance		*P*
	Incomplete (*n*=71), *n* (%)	Complete (*n*=201), *n* (%)	
Histopathology			
PCT	54 (26.1)	153 (73.9)	0.957 (F)
FCT	5 (23.8)	16 (76.2)	
HRV PCT	12 (27.3)	32 (72.7)	
Focality			
Unifocal	38 (22.0)	135 (78.0)	0.040 (C)
Multifocal	33 (33.3)	66 (66.7)	
Tumor-stage			
1a	3 (8.6)	32 (91.4)	0.013 (F)
1b	10 (19.2)	42 (80.8)	
2	39 (29.1)	95 (70.9)	
3	19 (37.3)	32 (62.7)	
Nodal status			
0	26 (17.4)	123 (82.6)	0.001 (F)
1a	13 (28.9)	32 (71.1)	
1b	32 (41.0)	46 (59.0)	
ETE			
Absent	49 (24.9)	148 (75.1)	0.454 (C)
Present	22 (29.3)	53 (70.7)	
Baseline Tg (ng/mL)			
>1	66 (31.4)	144 (68.6)	<0.001 (C)
<1	5 (8.1)	57 (91.9)	
Baseline Tg (ng/mL)			
>10	58 (47.9)	63 (52.1)	<0.001 (C)
<10	13 (8.6)	138 (91.4)	

C: Chi-square test, ETE: Extrathyroidal extension, FCT: Follicular carcinoma thyroid, F: Fisher's exact test, HRV: High-risk variants, PCT: Papillary carcinoma thyroid, T: Tumor, Tg: Serum thyroglobulin

factors that aid in the risk-stratification of DTC patients at the time of diagnosis and during the initiation of therapy are the size of primary tumors, status of gross extrathyroidal extension, and distant metastasis. Furthermore, multifocality and high-risk variants of thyroid carcinoma on histopathology add to the risk stratification at this stage, aiding in prognostication and further decision-making regarding the subsequent treatment. However, a proportion of patients who do not have any of these known high-risk factors might still exhibit aggressive disease with poor therapeutic responsiveness, suggesting the inadequacy of these clinicoradiological characteristics in predicting the aggressive course of DTC.[16]

Although a group of experts recommends the genetic testing in this regard, not many centers have the facility and expertise to carry out it optimally.[20] These lacunae have led the researchers to study immunophenotypes of thyroid cancer, for their prognostication and therapeutic planning, as this approach has already produced promising results in other solid tumors.[21-24] As per these emerging concepts, the lymphocytes play a central role in the immunological fight against the cancer cells, and the abundance of these lymphocytes at the tissue level is an important prognostic factor for therapeutic responsiveness.[23-25] Considering these observations, several researchers have evaluated if the relative concentration of lymphocytes in peripheral blood can be of any value in predicting the prognosis and therapeutic responsiveness of DTC.[6-8,25-27] The present study evaluates the association of NLR and LMR with the therapeutic responsiveness, in a cohort of DTC which otherwise lack overt high-risk clinicopathological predictors like gross extrathyroidal extension and distant metastasis.

Table 4: Association of neutrophil-to-lymphocyte ratio and lymphocyte-to-monocyte ratio with known predictors of outcomes

	Count	Median	IQR		*P*
			Lower	Upper	
NLR					
Histology					
PCT	207	2.52	1.81	3.77	0.631 (K)
FCT	21	2.93	1.73	4.07	
HRV PCT	44	2.53	1.64	3.77	
Focality					
Unifocal	173	2.43	1.74	3.89	0.522 (M)
Multifocal	99	2.71	1.81	3.59	
Tumor-stage					
1	35	2.42	1.77	4.41	0.619 (K)
2	52	2.27	1.70	3.68	
3	134	2.86	1.83	4.07	
4	51	2.48	1.74	3.51	
Nodal status					
0	149	2.40	1.75	3.58	0.725 (K)
1a	45	2.46	1.72	3.89	
1b	78	2.94	1.88	4.61	
ETE					
Absent	197	2.46	1.78	3.85	0.751 (M)
Present	75	2.63	1.77	4.05	
Baseline Tg					
>1	210	2.53	1.77	3.85	0.505 (M)
<1	62	2.72	1.77	3.90	
LMR					
Histology					
PCT	207	3.62	2.50	4.70	0.255 (K)
FCT	21	3.56	2.08	4.53	
HRV PCT	44	3.99	2.83	4.87	
Focality					
Unifocal	173	3.89	2.46	4.83	0.176 (M)
Multifocal	99	3.53	2.53	4.57	
Tumor-stage					
1	35	3.77	2.59	4.97	0.326 (K)
2	52	4.08	2.53	4.73	
3	134	3.51	2.37	4.61	
4	51	3.93	2.74	5.14	
Nodal status					
0	149	3.79	2.69	4.67	0.817 (K)
1a	45	3.42	2.22	5.02	
1b	78	3.52	2.28	4.70	
ETE					
Absent	197	3.58	2.49	4.69	0.546 (M)
Present	75	3.89	2.42	4.79	
Baseline Tg					
>1	210	3.75	2.47	4.80	0.127 (M)
<1	62	3.64	2.53	4.63	

ETE: Extrathyroidal extension, FCT: Follicular carcinoma thyroid, HRV: High-risk variants, K: Kruskal–Wallis, LMR: Lymphocyte to monocyte ratio, M: Mann–Whitney test, NLR: Neutrophil–to-monocyte ratio, PCT: Papillary carcinoma thyroid, Tg: Serum thyroglobulin, IQR: Interquartile range

The elevated NLR of 2.4 and above were associated with increased risk of incomplete disease clearance at 6 months in our cohort of low- and intermediate-risk DTC. The optimal cut-off of NLR obtained by the ROC curve is in agreement with the other literature-reported cut-off of NLR to predict the aggressive disease, which varies between 2.11 and 2.5.[9,15,28,29] These studies have also reported the correlation between the NLR with the other prognostic factors such as lymph node positivity, tumor size, multifocality, extrathyroidal extension elevated Tg, and risk of recurrence.[15,28-32] Although we could not establish the statistical significance in this regard, the NLR did demonstrate a trend of association with several of these factors. Interestingly, a few other studies have also reported the lack of correlation between the known risk factors and the NLR, despite the NLR being a predictor of prognosis in the same cohort.[7,8]

Similarly, the LMR has also shown a significant association with the status of disease clearance at 6 months in our study. The patients with complete disease clearance had a median LMR of 3.93 or above, as compared to that of 3.13 in those with incomplete disease clearance. The ability of preoperative low LMR in predicting the prognosis in our cohort has been comparable with the other reports too, and even in low and intermediate-risk PTC patients.[11,13,33]

A few other inflammatory markers-based predictors, which have been evaluated for their reliability in DTC include, platelet distribution width (PDW), PDW-to-platelet count ratio, platelet-to-lymphocyte ratio, plateletcrit, mean platelet volume, fibrinogen, and monocyte to high-density lipoprotein cholesterol ratio.[10,25,34-36] Although the results have been encouraging, the calculations and interpretations of these ratios are relatively complex when compared to the NLR and LMR, making the latter ratios the most preferred.

The present study also sheds light on the relevance of such markers in a cohort of Indian patients, who otherwise are exposed to peculiar socio-cultural risk factor prevalent in this region in the form of tobacco chewing, which is known to affect the inflammatory response. However, we have not analyzed the tobacco chewing as an independent determinant of NLR and LMR in this study.

Conclusions

The NLR and LMR can provide potential prognostic information on the short-term outcome in DTC. Their influence on the long-term disease outcome needs to be evaluated.

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Conflicts of interest

There are no conflicts of interest.

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