RESEARCH ARTICLE

A comparison of haemogram parameters of patients with thyroid papillary cancer and nodular goiter in Van, Turkey

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Abstract

Objective: To compare the haemogram parameters of patients with thyroid papillary cancer and nodular goiter.

Methods: The retrospective comparative study was conducted at Van Training and Research Regional Hospital, Van, Turkey, and comprised data of patients who underwent thyroidectomy from 2011 to 2015. The data was compared between patients with papillary thyroid cancer (group 1) and those with nodular hyperplasia (group 2) in terms of age, gender and thyroid stimulating hormone level as well as haemogram parameters, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. SPSS 20 was used for statistical analysis.

Results: Of the 90 patients, 53(59%) were in group 1 with papillary thyroid cancer and 37(%) in group 2 with nodular hyperplasia. Platelet-lymphocyte ratio was significantly higher in group 1 ($p=0.015$). Mean platelet volume was significantly higher in group 1 patients with a diameter of 1cm or more ($p<0.05$). Within group 1, lymphocyte count was significantly high in patients with invasion ($p<0.05$). In correlation analysis, group 1 patients with a tumour diameter of 1cm or more showed a significant correlation in mean platelet volume, tumour multicentricity, lymphocyte count, vascular invasion, thyroglobulin, platelet distribution width, platelet number and tumour multicentricity ($p<0.05$).

Conclusion: Only platelet-lymphocyte ratio could assist in distinguishing benign goiter from thyroid cancer. Also, mean platelet volume, lymphocyte count, and platelet distribution width appeared to be effective prognostic markers for papillary thyroid cancer.

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Introduction

Papillary thyroid cancer (PTC) has relatively good prognosis. Even so the extrathyroid invasion of adjacent soft tissues is present in nearly 15% patients (range 534%) at the first surgery. About a third of PTC patients have clinically evident lymphadenopathy. Only 1-7% PTC patients have distant metastases at diagnosis.[1] Besides in 20-year follow-up, postoperative nodal metastasis development is 9%, local recurrence 5%, distant metastasis 4% and 20-year cancer-specific mortality 5%.[2] Therefore, special attention is required in terms of diagnosis and follow-up.

Malignant cells are associated with lymphocytes, leucocytes and platelets, resulting in a systemic inflammatory response.[3,4] Platelet indices, such as platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), and neutrophil-lymphocyte ratio (NLR) are significant in most types of cancer.[5,6] There are very few publications in literature investigating the relation between TPC and PLR. The current study was planned to compare the haemogram parameters of patients with TPC and nodular goiter.

Materials and Methods

The retrospective at the Department of Endocrinology, Van Training and Research Regional Hospital, Van, Turkey, after approval from the unstitutional review board. Data ofpatients who underwent thyroidectomy from 2011 to 2015 was screened from the Pathology Department's record. Data related to PTC patients (group 1) and those with with nodular hyperplasia (NH) (group 2). Age, gender, thyroid stimulating hormone (TSH) levels were noted. PTC patients were graded according to the tumour nodule

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metastasis (TNM) stages of the American Joint Committee on Cancer (AJCC)[7] and only those with stage 1 were included as the number of patients graded to have other stages were insufficient and they were excluded. Also excluded were those aged below 18 years, those with clinical-subclinical hypothyroidism or clinical hyperthyroidism (TSH≥ 4.4mIU/ml or <0.19mIU/ml), diabetes, another cancer, inflammatory disease, myeloproliferative disorders, any organ insufficienty, infection or suspicion of infection, anaemia, or those taking anticoagulant medicine and alcohol. Apart from clinical and laboratory data, haemogram results of the day before thyroidectomia were noted and subsequently compared between the groups. Haemogram parameters were analysed using Automated Haematology Analyzer Sysmex XN 1000 device. TSH levels were examined in COBAS C 601 device with chemiluminescent method.

The tumour focus number, tumour location, thyroid capsule invasion, vascular invasion, lymph node metastasis, whether the patient received radioactive iodine therapy (RAI) after the operation, and the last recorded thyroglobulin levels were listed from clinical records of PTC patients. Electrochemiluminescence immunoassay analyser (ECLIA) immunological test was applied in Thyroglobulin e602 Roche device.

SPSS 20 was used for statistical analysis. Values were reported as means ± standard deviation. Frequencies and percentages were compared using Chi-square or Fisher's exact test. The level of significance was established by using Student t-test for normality. Correlation analysis was determined by using Spearman's rank correlation coefficient. Linear regression analysis was done at appropriate stages. Receiver-operating characteristic (ROC) analysis was conducted to specify the best cut-off value to predict the outcome when it was necessary. Differences were taken as significant at $p<0.05$.

Results

Of the 141 records analysed initially, 51(36.2%) were exluded. The sample, as such, had 90(63.8%) patients, 53(59%) were in PTC group 1 and 37(41%) in NH group 2. In group 1, there were 49(92.5%) female patients, while in group 2, there were 33(89.2%) females. The age range in group 1 was 19-68 years compared to 19-66 years in group 2 (Table 1).

Thyroglobulin levels of 23(43%) PTC patients ranged 0.04-0.54ng/ml and 34(64%) received postoperative RAI.

Table-1: Comparison of age, tumour and nodule diameter, TSH level with Student T test and gender with chi square test.

	Papillary thyroid carcinoma	Nodular hyperplasia	*p*-values
Age	n=53	n=37	0.29
mean ± SD:	38±11.6	40.7±12.3	
median (min-max):	19-68	19-66	
Gender	Male:4 Female:49	Male:4 Female:33	0.71
Tumour or nodule diameter (cm)	n=51	n=35	0.001
mean ± SD:	1.48±1.28	2.5±1.5	
median (min-max):	0.1-7	0.4-7.5	
TSH (µU/ml)	n=53	n=37	0.49
mean ± SD:	1.36± 0.88	1.48± 0.64	
median (min-max):	0.19-4.4	0.8-3.67	

TSH: Thyroid stimulating hormone, SD: Standard deviation

Table-2: Disease charactheristics of patients with papillary thyroid carcinoma group.

Patients with papillary thyroid carcinoma (n=53)	
Thyroglobulin (ng/ml)	n=23
mean ± SD:	0.23±0.11
median (min-max):	0.04-0.54
T1	
Tumour(≤2cm)	38
T2 Tumour(≤4cm)	11
T3 Tumour(>4cm)	2
Multicentricity	n=53
Present	23
Absent	28
Thyroid capsule invasion	n=35
Present	9
Absent	26
Lymphovascular invasion	n=48
Present	10
Absent	38

SD: Standard deviation

In 23(43.3%) PTC cases, tumour diameter was <1cm (range: 0.1-0.9cm) and in 30(56.7%) cases, the diameter was ≥1cm (range: 1-7cm). Nodule diameters of NH cases ranged 0.4-7.5cm, and the diameters of PTC patients were significantly lower than NH patients (p: 0.001.

In PTC patients, tumour localisation, tumour focus, lymph node metastasis and vascular invasion were noted (Table 2).

There was no significant difference between the groups in terms of NLR, MPV, haemoglobin, PC, neutrophil count (NC), lymphocyte count (LC), red blood cell distribution width (RDW), platelet crit (PCT) and PDW ($p>0.05$ each). However, there was significant relationship between the level of PLR and PTC ($p=0.015$) (Table 3).

ROC analysis showed that the area under the curve (AUC)

Table-3: Comparison of hemogram parameters between groups with Student T test.

	Papillary thyroid carcinoma	Nodular hyperplasia	*p*-values
Neutrophil count (cells/μl)	n=53	n=37	0.10
Mean ± SD	3964±1310	4470±1579	
Median (min-max)	1800-7300	1800-9770	
Lymphocyte count (cells/μl)	n=53	n=37	0.17
Mean ± SD	2163±467	2308±533	
Median (min-max)	1110-3610	1300-3380	
Neutrophil-to-lymphocyte ratio	n=53	n=37	0.61
Mean ± SD	1.90±0.80	1.99±0.82	
Median (min-max)	0.9-5.62	1.05-4.89	
Platelet count (cells/μl)	n=53	n=37	0.062
Mean ± SD	265981±57340	241783±63289	
Median (min-max)	132000-408000	147000-351000	
Platelet-to-lymphocyte ratio	n=53	n=37	0.015
Mean ± SD	126.82±32.16	109.31±34.18	
Median (min-max)	58.28-228.46	49.67-191.54	
Mean platelet volume (fl)	n=53	n=37	0.15
Mean ± SD	7.93±1.92	8.53±1.98	
Median (min-max)	3.3-12.6	3.1-11.8	
Platelet distribution width (%)	n=41	n=24	0.84
Mean ± SD	15.87±1.23	15.92±0.42	
Median (min-max)	10-17.8	15.2-17	
Plateletcrit (%)	n=31	n=23	0.28
Mean ± SD	2.50±0.35	2.63±0.48	
Median (min-max)	1.76-3.02	1.74-3.75	
Red blood cell distribution width ()	n=41	n=10	0.83
Mean ± SD	11.9±16	12.3±14.7	
Median (min-max)	13.47-0.93	13.54-0.80	
Haemoglobin (g/dl)	n=53	n=37	0.67
Mean ± SD	14.15±1.27	14.04±1.09	
Median (min-max)	12-17.6	12.10-17	

SD: Standard deviation

for PLR was 63.8% (Figure), the threshold value was 117.14, sensitivity 64%, specificity 59%, positive predictive value (PPV) 69% and negative predictive value (NPV) 53%.

PLR had positive relation with NLR (p=0.00) and negative relation with PDW (p-0.00). In regression analysis, NLR had significant effect on PLR (p=0.00). Thyroglobulin level was not significant but it affected NLR (p=0.063).

When tumour diameters were compared, MPV was significantly higher (p=0.014) in patients with a diameter >1cm. Also, vascular invasion was significantly higher in patients with a diameter >1cm (p=0.004).

In correlation analysis, patients with tumour diameter >1cm showed meaningful same direction correlation in MPV and tumour multicentricity, LC and vascular invasion, thyroglobulin and PDW, platelet number and tumour multicentricity, platelet number and PCT (p<0.05 each)). The correlation between the number of platelets and PDW

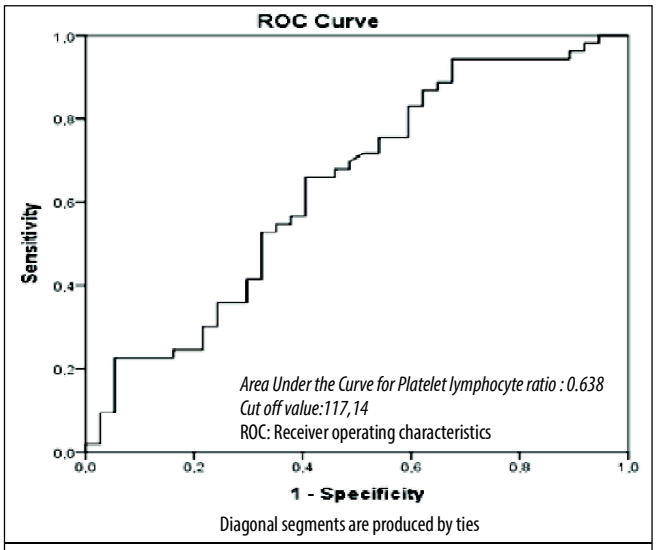

Figure: ROC analysis of Platelet-lymphocyte ratio (PLR).

was in the reverse direction (p<0.05).

PLR and PDW were higher in PTC cases but not significantly (p>0.05).

In patients with tumour diameter <1cm there was a significant increase in PLR (p=0.018) and significant decrease in MPV (p=0.018).

When the single tumour focus, was compared with multicentricity, there was a slight increase in PC in multicentricity (p=0.085).

In the PTC group, the number of lymphocytes was significantly higher in those with thyroid capsule invasion (p=0.045). Also, lymphocyte count was significantly increased in PTC patients with lymphovascular invasion (p=0.009). In ROC analysis, AUC was 0.73, threshold value 2255/mm3, sensitivity 80%, specificity 53%, PPV 42% and NPV 93%).

MPV was significantly higher who recived RAI than those who did not (p=0.046). In these patients, diameter, multicentricity and vascular invasion were also significantly higher (p<0.05 each). ROC analysis of MPV in these patients showed AUC was 0.66, threshold value 7.45, sensitivity 67%, specificity 42%, PPV 74% and NPV 50%.

Discussion

Systemic inflammation is reported to be effective on oncogenesis, proliferation, migration, angiogenesis and anti-tumour immunity via chemokines.[8] There is strong evidence for the role of inflammatory cells such as macrophages, neutrophils, lymphocytes, which interact

with the microenvironment in tumorigenesis.[9,10] Literature demonstrates that increased NLR is significantly related with PTC.[11] A study found NLR to be higher in patients with papillary cancer than other groups.[12]

One study stated that NLR was not significant in malignant and benign differentiation of thyroid tumoral formations. Five-year disease-free survival was shorter in stage 3 and 4 patients, and in PTC cases with higher NLR.[13] Gong et al. demonstrated an association between multiple foci, lymph node metastasis, tumour diameter, advanced stage and high NLR.[14] In another study, NLR was detected higher in stage 3-4 PTC patients than stage 1-2.[15] Lang et al. found no association between NLR and disease-free survival in PTC patients.[16]

In one study, NLR wasn't significantly different in patients with PTC compared to the control group.[17] In a study, NLR did not differ in patients with thyroid cancer and those with follicular adenoma. However, it was reported that high NLR was associated with large tumour diameter and more recurrence in patients with differentiated thyroid cancer.[18] We did not find a significant association of diagnosis and prognosis between NLR and PTC.

In literature, there are only a few researches in line with our study about the identification of the diagnostic associations between NLR and PTC, while there are more studies on prognosis. In one study, the size of the primary thyroid tumour and lymphovascular invasion did not significantly affect any of the platelet indices, NLR and white blood cell (WBC) count. In the same study, there was a significant increase in platelet count in cases with T3 tumours which were more than 4cm in diameter or extended beyond the thyroid capsule when compared to T1, T2 tumours. The study emphasised the high level of PC, PCT, PLR and the NPV of low PDW for extrathoracic extension.[19]

In a study of patients with differentiated thyroid carcinoma, both NLR and PLR were significantly higher in the study group than the controls, and the association with high thyroglobulin levels was presented, suggesting association with prognosis.[20]

A study has indicated that PLR may better predict inflammation than NLR in the end-stage renal disease (ESRD).[21] One study found that PLR was significantly higher in patients with tumour diameter >1cm when compared to the other PTC group. As a result of subgroup analysis, preoperative high PLR level was found to be associated with the development of lateral lymph node metastasis.[22]

As a result of our study, it can be suggested that PLR is more meaningful in terms of separating benign and malign neoplasms of the thyroid. Only early-stage PTC patients were included in our study and the analysis showed that PLR was significantly higher in PTC patients than NH patients. In ROC analysis, the optimal threshold value was 117.14.

When a study compared the PTC group with the benign goiter, only PDW was significantly lower in the platelet indices. However, we did not find any diagnostic significance and found a positive correlation between thyroglobulin level and PDW in PTC patients with a tumour diameter of 1cm or more. There was also a positive correlation between the multiple foci, MPV and PC in the same analysis. PTC cases with tumour size of 1cm or greater were compared with NH group and as a result the PDW was non-significant, however it was higher in the PTC group.

A study stated that the MPV level above 7.81 fl was riskier in terms of papillary cancer.[23] In our study, MPV levels were not different between the groups.

Although we did not find any diagnostic relationship between MPV and PTC, subgroup analysis of the PTC group showed that MPV of patients with primary tumour diameter of 1cm or more were significantly higher than those of smaller-sized PTCs. We found MPV in RAI-treated patients to be significantly higher than the untreated group. Besides, as a result of ROC analysis, the threshold value was stated as 7.45. All this suggests that it can be developed as a prognostic marker of PTC.

The comparative analysis of patients with and without thyroid capsule invasion in our study stated that lymphocyte count was significantly higher in the capsule invasion group. Also, the number of lymphocytes was significantly higher in patients with lymphovascular invasion and the optimal threshold value was 2255.

The current study has a retrospective design and a small smaple size which are its limitations. There is a need for a prospective study with larger patient population to verify the data.

Conclusion

WBC and platelet indices, except PLR, cannot assist in distinguishing benign goiter from thyroid cancer. MPV, PDW and lymphocyte number seemed to be effective as

prognostic factors for PTC.

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