RESEARCH

Lymph node ratio is superior to AJCC N stage for predicting recurrence in papillary thyroid carcinoma

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Abstract

Objective: Recently, lymph node ratio (LNR) has emerged as an alternative to American Joint Committee on Cancer (AJCC) N stage, with superior prognostic value. The utility of LNR in Middle Eastern papillary thyroid carcinoma (PTC) remains unknown. Therefore, we retrospectively analyzed a large cohort of 1407 PTC patients for clinicopathological associations of LNR.

Methods: Receiver operating characteristics (ROC) curve was used to determine the cut-off for LNR. We also performed multivariate logistic regression analysis to determine whether LNR or AJCC N stage was superior in predicting recurrence in PTC.

Results: Based on ROC curve analysis, a cut-off of 0.15 was chosen for LNR. High LNR was significantly associated with adverse clinicopathological characteristics such as male sex, extrathyroidal extension, lymphovascular invasion, multifocality, bilateral tumors, T4 tumors, lateral lymph node (N1b) involvement, distant metastasis, advanced tumor stage, American Thyroid Association (ATA) high-risk category and tumor recurrence. On multivariate analysis, we found that LNR was a better predictor of tumor recurrence than AJCC N stage (odds ratio: 1.96 vs 1.30; *P* value: 0.0184 vs 0.3831). We also found that LNR combined with TNM stage and ATA risk category improved the prediction of recurrence-free survival, compared to TNM stage or ATA risk category alone.

Conclusions: The present study suggests LNR is an independent predictor of recurrence in Middle Eastern PTC. Integration of LNR with 8th edition AJCC TNM staging system and ATA risk stratification will improve the accuracy to predict recurrence in Middle Eastern PTC and help in tailoring treatment and surveillance strategies in these patients.

Key Words

- papillary thyroid carcinoma
- lymph node ratio
- recurrence
- lymph node stage
- ATA risk category

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Introduction

Papillary thyroid carcinoma (PTC) is the commonest subtype of thyroid cancer, accounting for 80–90% of all thyroid cancers, and is generally associated with favorable outcome (1, 2). The incidence of PTC has increased significantly in recent years (3, 4). In Saudi Arabia, PTC is very common among females and ranks second after breast cancer (5). Although PTC has a favorable outcome, 3–10% of patients demonstrated recurrent disease within the first decade after treatment (6, 7). Accurate PTC staging is an important process to help

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clinicians pursue the best therapeutic options for their patients.

American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used staging system for thyroid cancer. AJCC nodal (N) stage in PTC is sub-divided based on the anatomical location of lymph node (LN) metastasis, being classified as central LN (N1a) or lateral LN (N1b) metastasis (8). Although it has been reported that LN involvement can impact a patient's prognosis and increase the risk of recurrence as well as distant metastasis (9, 10, 11, 12, 13, 14), the association of N stage with clinicopathological markers and prognosis has not been fully explored in PTC from Middle Eastern ethnicity.

In addition, using N stage classification only might underestimate the significance and the extent of the burden of the disease since it is based solely on anatomical location of LN metastasis. An additional emerging prognostic factor in PTC is the lymph node ratio (LNR) (15, 16, 17, 18). The LNR, which is defined as the number of LNs showing metastatic deposits divided by the number of LN resected, is suggested to be a superior prognostic variable, better-reflecting tumor burden and recurrence prediction (19, 20, 21, 22).

Disease recurrence is the most relevant oncologic outcome in PTC since the mortality rate from PTC is very low (23, 24). To date, whether the LNR works better than the 8th AJCC N staging in predicting recurrence in Middle Eastern PTC remains unknown. In this study, we retrospectively enrolled 1407 PTC patients with clinicopathological and follow-up information and compared the effectiveness of AJCC 8th edition N staging and LNR in predicting the recurrence of PTC patients from Middle Eastern ethnicity.

Materials and methods

Patient selection

One thousand five-hundred fifteen consecutive unselected PTC patients diagnosed between 1988 and 2018 at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) were available to be included in the study. Patients in whom regional LN could not be evaluated (Nx) were excluded from the study ($n = 108$). A total of 1407 PTC cases were included for analysis. Cases were identified based on clinical history followed by fine-needle aspiration cytology for confirmation. The Institutional Review Board, King Faisal Specialist Hospital and Research Centre approved this study and the Research Advisory Council (RAC) provided waiver of consent under projects RAC #2211168 and RAC #2110031.

Clinicopathological data

Baseline clinicopathological data were collected from case records and have been summarized in Table 1. Based on the American Thyroid Association (ATA) guidelines, tall cell, hobnail, columnar cell, diffuse sclerosing and insular variants were classified as aggressive variants, whereas classical and follicular variants were classified as non-aggressive variants (25). Staging of PTC was performed using the eighth edition of the AJCC staging system. Only structural recurrence (local, regional or distant) was considered for analysis. Recurrence was defined as any newly detected tumor (local or distant) or metastatic regional LN based on ultrasound and/or imaging studies in patients who had been previously free of disease following initial treatment. Radioactive iodine (RAI) refractory disease and risk categories were defined based on 2015 ATA guidelines (25).

Lymph node ratio cut-off

LNR was defined as the number of metastatic LNs divided by the number of LNs resected. To determine the cut-off value for LNR, we used the receiver operating characteristic (ROC) curve analysis. Using recurrence-free survival as the outcome, we calculated the area under curve (AUC), sensitivity, specificity and 95% CIs. We found that LNR of 0.15 was related to tumor recurrence with AUC of 0.668, sensitivity of 69% and specificity of 59% ($P < 0.001$; Fig. 1). Hence, a cut-off of 0.15 was chosen for analysis of clinicopathological associations of LNR.

BRAF and *TERT* mutation analysis

BRAF and *TERT* mutation data was assessed in our laboratory by Sanger sequencing and has been published by us previously (26, 27).

PD-L1 immunohistochemistry

PD-L1 immunohistochemical staining and analysis were performed by us previously in PTC (26). Briefly, tissue microarray slides were processed and stained manually. Primary antibody against PD-L1 (E1L3N, 1:50 dilution, pH 9.0, Cell Signaling Technology) was used. A membranous and/or cytoplasmic staining was observed. Only the

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Table 1 Patient characteristics of the study cohort.

	Overall cohort (n = 1407)	
Age at diagnosis (years)		
Median (range)	37.7 (6.0–88.0)	
<55	1160	82.4
≥55	247	17.6
Gender		
Male	333	23.7
Female	1074	76.3
Histologic subtype		
Classical variant	948	67.3
Follicular variant	239	17.0
Tall cell variant	126	9.0
Other variants	94	6.7
Extrathyroidal extension		
Present	621	44.1
Absent	786	55.9
Lymphovascular invasion		
Present	298	21.2
Absent	1109	78.8
Tumor focality		
Unifocal	709	50.4
Multifocal	698	49.6
Tumor laterality		
Unilateral	950	67.5
Bilateral	457	32.5
Surgical margin		
Positive	387	27.5
Negative	1020	72.5
pT		
T1	564	40.2
T2	452	32.2
T3	271	19.3
T4	117	8.3
Regional LN metastasis		
N0	661	47.0
N1a	206	14.6
N1b	540	38.4
pM		
M0	1332	94.7
M1	75	5.3
TNM stage		
I	1176	83.7
II	156	11.1
III	22	1.6
IV	51	3.6
BRAF mutation		
Present	768	54.6
Absent	613	44.6
Unknown	26	1.8
TERT mutation		
Present	181	12.9
Absent	1124	79.9
Unknown	102	7.2
PD-L1 IHC		
Positive	435	32.7
Negative	896	67.3
Initial surgery		
Lobectomy	220	15.6
Total thyroidectomy alone	374	26.5
Total thyroidectomy with central neck dissection	813	57.9
RAI given		
Yes	1185	84.2
No	222	15.8
RAI refractory		
Yes	244	20.6
No	941	79.4
Recurrence		
Yes	275	19.5
No	1132	80.5
ATA risk category		
Low	231	16.4
Intermediate	460	32.7
High	716	50.9

membrane staining was considered for scoring. PD-L1 was scored as described previously (28). Briefly, the proportion of positively stained cells was calculated as a percentage for each core and the scores were averaged across two tissue cores from the same tumor to yield a single percent staining score representing each cancer patient. For the purpose of statistical analysis, the scores were dichotomized.

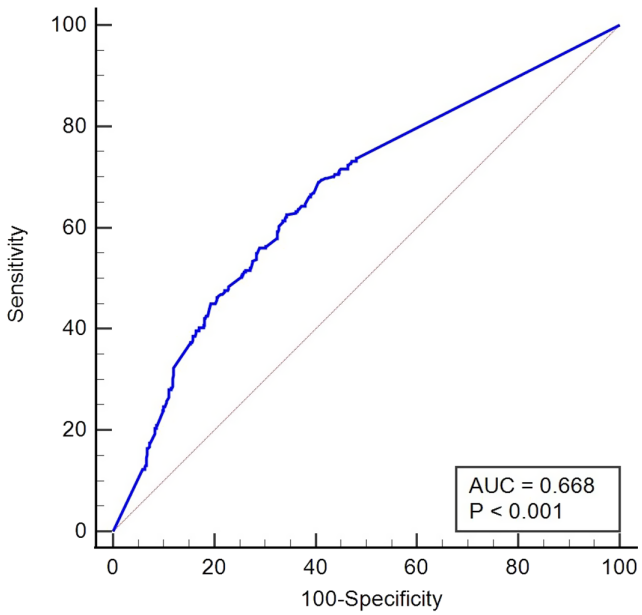

Figure 1
Receiver operating characteristic (ROC) curve for lymph node ratio (LNR). Tumors with LNR of 0.15 predicted PTC recurrence with a sensitivity of 69%, specificity of 59% and area under cover (AUC) of 0.668 (P < 0.001).

Cases showing the expression levels of ≥5% were classified as overexpression and those with less than 5% as low expression.

Follow-up and study endpoint

Patients were regularly followed by both physical examinations and imaging studies to identify tumor recurrence. The median follow-up was 9.2 years (range 1.0–30.1 years). Recurrence-free survival (RFS) was defined as the time (in months) from date of initial surgery to the occurrence of any tumor recurrence (local, regional or distant). In case of no recurrence, date of last follow-up was the study endpoint for RFS.

Statistical analysis

The associations between clinicopathological variables was performed using contingency table analysis and chi-square tests. Cut-off for LNR was determined using the ROC curve. Logistic regression was used for multivariate analysis. Two-sided tests were used for statistical analyses with a limit of significance defined as P value < 0.05. All data analyses, except ROC curve analysis, were performed using the JMP14.0 (SAS Institute, Inc., Cary, NC) software package. ROC curve analysis was performed using MedCalc software, version 10.4.7.0 for Windows (MedCalc, Ostend, Belgium).

Results

Patient and tumor characteristics

Median age of the study cohort was 37.7 years (range 6.0–88.0 years), with a male: female ratio of 1: 3.2. Classical variant PTC was the predominant histologic subtype, accounting for 67.3% (948/1407) of all cases, followed by follicular variant (17.0%; 239/1407) and tall cell variant 9.0% (126/1407). Extrathyroidal extension was noted in 44.1% (621/1407) of cases and lymphovascular invasion in 21.2% (298/1407). 49.6% (698/1407) of PTCs were multifocal and 32.5% (457/1407) were bilateral. Tumor recurrence was noted in 19.5% (275/1407) of the entire cohort (Table 1). The median time to first recurrence from initial surgery in our cohort was 2.6 years (range 0.6–19.8 years). The median number of LNs removed was 15 with the following N stage distribution: N0 (47.0%; 661/1407), N1a (14.6%; 206/1407), and N1b (38.4%; 540/1407) (Table 1). *BRAF* mutation was noted in 55.6% (768/1381) PTCs and *TERT* mutation was seen in 13.9% (181/1305). Both *BRAF* and *TERT* mutation data were available for 1299 patients in our cohort. Co-existence of *BRAF* and *TERT* mutation was noted in 10.5% (136/1299) of cases.

Incidence and clinicopathological associations of recurrence in PTC

Tumor recurrence was noted in 19.5% (275/1407) of PTCs during follow-up. Recurrence was significantly associated with adverse clinicopathological parameters, such as age ≥ 55 years (P < 0.0001), male sex (P < 0.0001), extrathyroidal extension (P < 0.0001), bilateral tumors (P < 0.0001), T4 tumors (P < 0.0001), LN metastasis (P < 0.0001), distant metastasis (P < 0.0001), advanced tumor stage (P < 0.0001), RAI refractory disease (P < 0.0001) and ATA high-risk category (P < 0.0001). On further division of N1 tumors into N1a and N1b, we found that 31.1% (168/540) of N1b tumors developed recurrence, compared to 17.0% (35/206) of N1a tumors. The difference in recurrence rate between N1a and N1b tumors was statistically significant (P = 0.0001) (Table 2).

Clinicopathological associations of LNR in PTC

Using a cut-off of 0.15, 44.8% (631/1407) of tumors had high LNR. Tumors exhibiting a high LNR were significantly associated with male sex (P = 0.0019), extrathyroidal extension (P < 0.0001), lymphovascular invasion (P = 0.0034), multifocality (P < 0.0001), bilateral tumors (P < 0.0001), T4 tumors (P < 0.0001), N1b (P < 0.0001), distant metastasis (P = 0.0006), advanced tumor stage (P = 0.0246), RAI refractory disease (P < 0.0001) and ATA high-risk category (P < 0.0001). We also found a significant association with tumor recurrence (P < 0.0001). Interestingly, high LNR was associated with *BRAF* mutation (P < 0.0001) and PD-L1 expression (P = 0.0031) (Table 3).

LNR is a better predictor of tumor recurrence than AJCC N stage

Since high LNR was associated with tumor recurrence, we sought to determine whether it could be used as an independent predictor of recurrence. Using multivariate logistic regression analysis, we found high LNR to be an independent predictor of recurrence (odds ratio = 1.96; 95% CI = 1.12–3.43; P = 0.0184), whereas LN stage was not

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Table 2 Clinicopathological associations of recurrence in papillary thyroid carcinoma.

	Total		Recurrence present		Recurrence absent		*P* value
	No.	%	No.	%	No.	%	
Total	1407		275	19.5	1132	80.5	
Age at surgery (years)							
<55	1160	82.4	188	68.4	972	85.9	<0.0001
≥55	247	17.6	87	31.6	160	14.1	
Gender							
Male	333	23.7	93	33.8	240	21.2	<0.0001
Female	1074	76.3	182	66.2	892	78.8	
Histologic subtype							
Classical variant	948	67.3	206	74.9	742	65.6	0.0026
Follicular variant	239	17.0	28	10.2	211	18.6	
Tall cell variant	126	9.0	26	9.5	100	8.8	
Other variants	94	6.7	15	5.4	79	7.0	
Extrathyroidal extension							
Present	621	44.1	185	67.3	436	38.5	<0.0001
Absent	786	55.9	90	32.7	696	61.5	
Lymphovascular invasion							
Present	298	21.2	57	20.7	241	21.3	0.8374
Absent	1109	78.8	218	79.3	891	78.7	
Tumor focality							
Unifocal	698	49.6	125	45.5	573	50.6	0.1242
Multifocal	709	50.4	150	54.5	559	49.4	
Tumor laterality							
Unilateral	950	67.5	154	56.0	796	70.3	<0.0001
Bilateral	457	32.5	121	44.0	336	29.7	
pT							
T1	564	40.2	99	36.1	465	41.1	<0.0001
T2	452	32.2	63	23.0	389	34.4	
T3	271	19.3	59	21.5	212	18.8	
T4	117	8.3	53	19.4	64	5.7	
pN							
N0	661	47.0	72	26.2	589	52.0	<0.0001
N1a	206	14.6	35	12.7	171	15.1	
N1b	540	38.4	168	61.1	372	32.9	
LN ratio							
≥ 0.15	631	44.9	184	66.9	447	39.5	<0.0001
< 0.15	776	55.1	91	33.1	685	60.5	
pM							
M0	1332	94.7	225	81.8	1107	97.8	<0.0001
M1	75	5.3	50	18.2	25	2.2	
TNM Stage							
I	1176	83.7	174	63.5	1001	88.6	<0.0001
II	156	11.1	66	24.1	90	8.0	
III	22	1.6	6	2.2	16	1.4	
IV	51	3.6	28	10.2	23	2.0	
BRAF mutation							
Present	768	55.6	160	59.7	608	54.6	0.1323
Absent	613	44.4	108	40.3	505	45.4	
TERT mutation							
Present	181	13.9	85	32.7	96	9.2	<0.0001
Absent	1124	86.1	175	67.3	949	90.8	
PD-L1 IHC							
Positive	435	32.7	111	42.2	324	30.3	0.0003
Negative	896	67.3	152	57.8	744	69.7	
RAI Refractory							
Yes	244	20.6	155	58.7	89	9.7	<0.0001
No	941	79.4	109	41.3	832	90.3	
ATA risk category							
Low	231	16.4	12	4.4	219	19.3	<0.0001
Intermediate	460	32.7	47	17.1	413	36.5	
High	716	50.9	216	78.5	500	44.2	

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Table 3 Clinicopathological associations of lymph node ratio (LNR) in papillary thyroid carcinoma.

	Total		LNR ≥0.15		LNR <0.15		*P* value
	No.	%	No.	%	No.	%	
Total	1407		631	44.8	776	55.2	
Age at surgery (years)							
<55	1160	82.4	527	83.5	633	81.6	0.3391
≥55	247	17.6	104	16.5	143	18.4	
Gender							
Male	333	23.7	174	27.6	159	20.5	0.0019
Female	1074	76.3	457	72.4	617	79.5	
Histologic subtype							
Classical variant	948	67.3	483	76.6	465	59.9	<0.0001
Follicular variant	239	17.0	48	7.6	191	24.6	
Tall cell variant	126	9.0	60	9.5	66	8.5	
Other variants	94	6.7	40	6.3	54	7.0	
Extrathyroidal extension							
Present	621	44.1	379	60.1	242	31.2	<0.0001
Absent	786	55.9	252	39.9	534	68.8	
Lymphovascular invasion							
Present	298	21.2	156	24.7	142	18.3	0.0034
Absent	1109	78.8	475	75.3	634	81.7	
Tumor focality							
Unifocal	698	49.6	272	43.1	426	54.9	<0.0001
Multifocal	709	50.4	359	56.9	350	45.1	
Tumor laterality							
Unilateral	950	67.5	370	58.6	580	74.7	<0.0001
Bilateral	457	32.5	261	41.4	196	25.3	
pT							
T1	564	40.2	219	34.8	345	44.6	<0.0001
T2	452	32.2	209	33.2	243	31.4	
T3	271	19.3	131	20.8	140	18.1	
T4	117	8.3	71	11.3	46	5.9	
pN							
N0	661	47.0	0	0.0	661	85.2	<0.0001
N1a	206	14.6	174	27.6	32	4.1	
N1b	540	38.4	457	72.4	83	10.7	
pM							
M0	1332	94.7	583	92.4	749	96.5	0.0006
M1	75	5.3	48	7.6	27	3.5	
TNM stage							
I	1176	83.7	506	80.4	670	86.3	0.0246
II	156	11.1	86	13.7	70	9.0	
III	22	1.6	12	1.9	10	1.3	
IV	51	3.6	25	4.0	26	3.4	
BRAF mutation							
Present	768	55.6	388	62.7	380	49.9	<0.0001
Absent	613	44.4	231	37.3	382	50.1	
TERT mutation							
Present	181	13.9	92	15.7	89	12.4	0.0934
Absent	1124	86.1	496	84.3	628	87.6	
PD-L1 IHC							
Positive	435	32.7	222	36.9	213	29.2	0.0031
Negative	896	67.3	380	63.1	516	70.8	
RAI refractory							
Yes	244	20.6	155	27.2	89	14.5	<0.0001
No	941	79.4	414	72.8	527	85.5	
Recurrence							
Yes	275	19.6	184	29.2	91	11.7	<0.0001
No	1132	80.4	447	70.8	685	88.3	
ATA risk category							
Low	231	16.4	1	0.2	230	29.6	<0.0001
Intermediate	460	32.7	226	35.8	234	30.2	
High	716	50.9	404	64.0	312	40.2	

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an independent predictor of recurrence (Odds ratio = 1.30; 95% CI = 0.72–2.35; P = 0.3831) (Table 4).

LNR combined with TNM stage and ATA risk category as a predictor of recurrence-free survival

We next sought to analyze whether LNR combined with TNM stage and ATA risk category could better predict RFS, compared to either of them alone. On multivariate Cox proportional hazards model, we found that compared to TNM stage alone, the hazard ratios of corresponding stage combined with LNR was higher (Table 5). Similarly, the hazard ratios of ATA risk category combined with LNR was higher, compared to the corresponding ATA risk category alone (Table 6). This suggests that combining LNR with TNM stage or ATA risk category was a better predictor of RFS compared to either of them alone.

Discussion

Cancer recurrence remains a major challenge for PTC patients. It is clinically important to identify markers that can accurately predict recurrence. Predicting tumor recurrence is needed to tailor the initial treatment and follow-up intensity. In this study, we first determined the tumor recurrence rate to be 19.5% (275/1407) in Middle Eastern PTC. This recurrence rate is relatively high (29, 30, 31) and highlights the urgent need to establish an accurate model to predict recurrence in PTC patients from Middle Eastern ethnicity. Interestingly, our cohort also presented with more aggressive disease, as evidenced by a high rate of aggressive variants (15.7%), multifocality (49.6%), extrathyroidal extension (44.1%) and a lower age at presentation (median, 38 years). This probably reflects the inherent aggressive nature of PTC in this ethnicity, as evidenced by other studies from this region, which also found a relatively high rate of aggressive variants (32, 33), multifocality (34, 35), extrathyroidal extension (32, 36) and a low median age at diagnosis (37, 38). However, it could also be partially attributed to the fact that ours is the foremost tertiary care center in the region and most advanced diseases are referred to our hospital from all over Saudi Arabia.

Tumor recurrence was significantly associated with advanced T stage (P < 0.0001). Surprisingly 17.6% (99/564) of pT1 tumors exhibited tumor recurrence, which is relatively higher in comparison to other studies where the recurrence rate in T1 is rare (39, 40, 41). Comparing within AJCC N stage subgroups, tumor recurrence was found to

Table 4 Multivariate logistic regression analysis for predictors of recurrence in papillary thyroid cancer.

	Recurrence					
	Univariate			Multivariate		
Clinicopathological variables	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age						
≥ 55 years (vs < 55 years)	2.81	2.07–3.81	<0.0001	2.56	1.74–3.77	<0.0001
Sex						
Male (vs female)	1.90	1.42–2.53	<0.0001	1.52	1.11–2.09	0.0094
Histology						
Aggressive variants (vs non-aggressive variants	0.93	0.65–1.35	0.7114			
Tumor laterality						
Bilateral (vs unilateral)	1.86	1.42–2.44	<0.0001	1.29	0.95–1.74	0.1012
Tumor focality						
Multifocal (vs Unifocal)	1.23	0.94–1.60	0.1248			
Extrathyroidal extension						
Present (vs Absent)	3.28	2.48–4.34	<0.0001	1.89	1.38–2.59	<0.0001
Lymphovascular invasion						
Present (vs Absent)	0.97	0.70–1.34	0.8378			
pT						
T3-4 (vs T1-2)	2.14	1.62–2.82	<0.0001	1.48	1.08–2.02	0.0154
Distant metastasis						
Present (vs absent)	9.84	5.96–16.24	<0.0001	7.49	4.02–13.94	<0.0001
TNM stage						
III–IV (vs I–II)	3.96	2.45–6.41	<0.0001	0.41	0.20–0.85	0.0170
LN metastasis						
Present (vs absent)	3.05	2.28–4.10	<0.0001	1.30	0.72–2.35	0.3831
LN ratio						
≥ 0.15 (vs <0.15)	3.09	2.35–4.09	<0.0001	1.96	1.12–3.43	0.0184

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Table 5 Univariate and multivariate analyses of baseline variables for recurrence-free survival with the TNM staging system.

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
8th TNM				
I	Reference		Reference	
II	3.985 (2.997–5.300)	<0.0001	4.250 (2.613–6.912)	<0.0001
III	3.030 (1.342–6.843)	0.0080	3.103 (1.180–8.165)	0.0220
IV	7.923 (5.286–11.873)	<0.0001	7.320 (3.759–14.252)	<0.0001
8-h TNM with LNR				
I with low LNR	Reference		Reference	
I with high LNR	3.628 (2.602–5.060)	<0.0001	2.958 (2.090–4.187)	<0.0001
II with low LNR	7.219 (4.499–11.581)	<0.0001	7.630 (3.812–15.273)	<0.0001
II with high LNR	9.423 (6.170–14.392)	<0.0001	8.857 (4.941–15.877)	<0.0001
III with low LNR	2.117 (0.292–15.344)	0.4580	2.220 (0.282–17.453)	0.4480
III with high LNR	10.646 (4.233–26.779)	<0.0001	9.516 (3.202–28.281)	<0.0001
IV with low LNR	18.018 (10.062–32.266)	<0.0001	17.423 (7.681–39.522)	<0.0001
IV with high LNR	15.309 (8.257–28.382)	<0.0001	12.560 (5.337–29.556)	<0.0001

be significantly more common in patients with N1b stage (31.1%, 168/540) as against patients with N1a (17.0%, 35/206) and N0 (10.9%, 72/661), as expected.

Although the 8th edition of AJCC TNM staging is commonly used to predict the patient's outcome, it has some limitations. Patients with PTC and LN metastasis are staged according to the presence or absence of LN metastasis in anatomic compartments. The extent of the disease is not considered in this staging system. There is growing evidence showing the value of considering the extent of LN metastasis in PTC prognosis (14, 42, 43, 44). The American Thyroid Association (ATA) risk stratification system now considers the size and number of LN metastasis as an important factor in risk stratification (25).

Recently, more tailored risk stratification using LNR was proposed as a more reliable prognosticator of recurrence in PTC. Recent investigations of LNR in PTC have suggested that it has prognostic significance in both the central as well as lateral LN metastasis and maybe superior to conventional AJCC staging (17, 45, 46). Others have suggested the integration of LNR to the current staging system to improve the prediction of recurrence in patients with PTC (18). For Middle Eastern PTC, the use of LNR as a predictive tool for recurrence has not previously been analyzed. In this study, using a cut-off of 0.15 for LNR, we were able to identify a subset of Middle Eastern PTC patients at high risk of tumor recurrence and that LNR was positively associated with adverse clinicopathological characteristics, such as male gender, multifocality, larger tumor size, extrathyroidal extension, bilateral tumors and RAI-refractiveness. We also noted a positive correlation between LNR and *BRAF* mutations as well as PD-L1 protein overexpression, which we previously have shown to have negative impact on Middle Eastern PTC (26, 47).

Interestingly, LNR of more than 0.15 was a strong independent predictor of tumor recurrence (odds ratio = 1.96; 95% CI = 1.12–3.43; $P = 0.0184$). Patients with LNR more than 0.15 exhibited a two-fold higher risk of recurrence, while the patient with N1 (using AJCC N staging) showed a 1.3-fold high risk of recurrence, suggesting that LNR was a better predictor of recurrence than the AJCC N stage. The fact that higher LNR increased the HR of the same stage tumor especially for TNM stage I (Table 5), is a strong indication of LNR predictive power

Table 6 Univariate and multivariate analyses of baseline variables for recurrence-free survival with ATA risk stratification.

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
2015 ATA risk category				
Low	Reference		Reference	
Intermediate	2.172 (1.152–4.097)	0.0170	2.195 (1.159–4.157)	0.0160
High	6.610 (3.696–11.822)	<0.0001	4.666 (2.502–8.704)	<0.0001
2015 ATA risk category with LNR				
Low with low LNR	Reference		Reference	
Intermediate with low LNR	0.700 (0.286–1.714)	0.7000	0.750 (0.306–1.839)	0.5300
Intermediate with high LNR	3.807 (1.992–7.275)	<0.0001	3.811 (1.981–7.330)	<0.0001
High with low LNR	4.964 (2.692–9.154)	<0.0001	3.793 (1.989–7.235)	<0.0001
High with high LNR	7.892 (4.380–14.220)	<0.0001	6.081 (3.230–11.447)	<0.0001

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of recurrence even in the early stage. Also, patients with high-risk ATA with LNR ≥0.15 had a much higher HR compared to the high-risk ATA category alone (6.08 vs 4.67; Table 6), further strengthening the importance of LNR as a predictor of recurrence. This is clinically very important since it indicates that LNR is the most suitable and valuable predictor for recurrence in PTC patients of Middle Eastern ethnicity and suggests that adding LNR to the 8th AJCC TNM staging and ATA risk stratification system should be considered by clinicians to increase the accuracy of predicting PTC recurrence in this population.

Our study included a large sample size from the Middle Eastern population allowing for adequate multivariable adjustment for patient and treatment characteristics. Also, this study is from a single institute, which helped in providing accurate and homogenous information such as gene mutations, type of therapy and length of follow-up. Despite the strength of this study, it is limited by its retrospective nature which could cause selection bias. Also, this study was conducted on PTC from a specific ethnicity and therefore further larger multicenter studies from other ethnicities are encouraged to make generalizable conclusions.

In conclusion, the present study suggests LNR is an independent predictor of recurrence in Middle Eastern PTC. Integration of LNR with 8th edition AJCC TNM staging system and ATA risk stratification will improve the accuracy to predict recurrence in Middle Eastern PTC and help in tailoring treatment and surveillance strategies in these patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Study concept and design: K S A, S K P, A K S. Executed the study: S K P, A K S, Z Q, S O A, F D, S A, F A D. Statistical analysis: Z Q. Drafting the article: K S A, A K S, S K P. Critical revision of the article for important intellectual content, writing of the article, and approval of the final version: K S A, S K P, A K S, Z Q, S O A, F D, S A, F A D.

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