



Risk factors for central and lateral lymph node metastasis in papillary thyroid carcinoma

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Background: Lymph node metastasis (LNM) is commonly observed in papillary thyroid carcinoma. This study aimed to investigate the risk factors for LNM in patients with papillary thyroid carcinoma.

Methods: The clinicopathological factors of 417 patients were investigated, and differences according to the presence or absence of LNM were evaluated.

Results: LNM was associated with age <55 years, male sex, tumor size >10 mm, multiple and bilateral tumors, tumor involving the lower pole or entire lobe, lymphovascular invasion (LVI), perineural invasion (PNI), and extrathyroidal extension (ETE). Univariable and multivariable analyses showed that age <55 years, male sex, tumor size >10 mm, LVI, and ETE were related to central LNM. Male sex, tumor size >10 mm, and LVI were correlated with lateral LNM ($p < 0.05$). Compared to central LNM, more lymph nodes were involved in metastases and the metastatic tumors were larger in lateral LNM. Extranodal extension (ENE) was more commonly observed in lateral LNM ($p < 0.001$) and was associated with tumor size >10 mm, multifocality, PNI, ETE, and the absence of lymphocytic thyroiditis ($p < 0.05$).

Conclusions: Younger age, male sex, tumor size >10 mm, LVI, and ETE were risk factors for central LNM, while male sex, tumor size >10 mm, and LVI were risk factors for lateral LNM. ENE was more commonly observed in lateral LNM, and tumor size >10 mm, multifocal tumors, PNI, ETE, and tumors unrelated to lymphocytic thyroiditis were risk factors for ENE.

Keywords: Extranodal extension; Lymph node metastasis; Papillary thyroid cancer; Risk factors

Introduction

Thyroid cancer is a common malignancy of the endocrine system, and the diagnosis and treatment rates have increased in Korea due to the activation of health examinations. Among thyroid cancer, 80% to 90% are papillary thyroid carcinoma (PTC) [1]. Although most patients with PTC have a good prognosis with a long-term survival rate of over 90% [2], PTC affects the patient's quality of life with

respect to local metastasis or recurrence. Regional lymph node metastasis (LNM) is the major factor in recurrence and reoperation [3,4]. LNM is common in PTC, with an incidence of 30% to 80% [4].

In general, for PTC with central neck LNM, thyroidectomy and central compartment lymph node dissection are recommended. However, it is not easy to predict LNM, and preoperative ultrasound can detect only 20% to 31% of central neck LNMs [5]. According to the American Thyroid

Received: October 17, 2022; **Revised:** November 7, 2022; **Accepted:** November 21, 2022

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Association guidelines, prophylactic central compartment lymphadenectomy is not recommended due to the low reliability of preoperative examinations [6].

In the course of routine pathology, we may find cases with significant LNM despite the small size of the tumor, and conversely, cases where no LNM is observed despite large tumor size. LNM usually develops first in the central compartment and later progresses to the lateral compartment [5]. However, skip metastasis, which skips the central compartment and immediately metastasizes to the lateral compartment, is also often observed. Therefore, analyzing and accurately predicting the risk factors for LNM can help to plan appropriate surgery and management and help to prevent a recurrence.

The aims of this study were to elucidate the clinicopathological differences of PTC according to the presence or absence of LNM and investigate factors that can predict LNM.

Methods

Ethical statements: This study was approved by the Institutional Review Board of Presbyterian Medical Center (IRB No. 2022-01-006). Patient consent was waived because this study was a retrospective review of pathological diagnoses in an operated sample, which had no effect on patients.

1. Patient selection

Patients who underwent surgery and histopathological examination for PTC at the Presbyterian Medical Center from March 2019 to December 2021 were selected through medical records. All age groups and tumor sizes were included. Classic type cases, as well as other types, were included. Patients with coexisting carcinomas such as follicular carcinoma were excluded. Cases with missing data were not included. The surgical policy was based on lobectomy or total thyroidectomy along with central lymph node dissection. Central lymph node dissection was performed prophylactically, regardless of preoperative ultrasound findings. Lateral lymph node dissection was performed for therapeutic purposes only if preoperative lateral LMN was suspected.

2. Clinical parameters

Data on age and sex were collected. Age was classified into two groups based on an age of 55 years according to

the criteria for staging differentiated thyroid cancer in the American Joint Committee on Cancer Cancer Staging Manual 8th edition [7].

3. Histopathologic parameters

Surgically removed specimens were examined by four pathologists and the following histopathologic parameters were evaluated: tumor size, location, multifocality, bilaterality, histologic subtype, lymphovascular invasion (LVI), perineural invasion (PNI), extrathyroidal extension (ETE), LNM, extranodal extension (ENE), and lymphocytic thyroiditis. The size of the tumor was evaluated by dividing them into two groups: those smaller than or equal to 10 mm and those larger than 10 mm. In the case of multiple tumors, only the size of the largest tumor was collected. Multifocality was defined as two or more tumors. LNM was subgrouped into central and lateral LNM. The diagnosis of lymphocytic thyroiditis was made when diffuse lymphocyte infiltration and fibrosis were observed throughout the thyroid gland regardless of the presence or absence of thyroid parenchymal atrophy. Immunohistochemical studies were performed to evaluate LVI and PNI.

4. Detection of LVI, PNI, and *BRAF* V600E mutation using immunohistochemistry

Immunohistochemistry was performed on 4- μ m-thick sections of formalin-fixed, paraffin-embedded tissue blocks. The antibodies used were mouse monoclonal antibody to CD34 (NCL-L-END, Novocastra; Leica Biosystems, Wetzlar, Germany), mouse monoclonal antibody to podoplanin (D2-40, Cell Marque; Sigma-Aldrich, St. Louis, MO, USA), rabbit polyclonal antibody to S-100 (NCL-L-S100p, Novocastra), and mouse monoclonal antibody to anti-BRAF V600E (VE1; Ventana Medical Systems, Oro Valley, AZ, USA). The Bond-Max automated immunostainer was used for CD34 and S-100 staining. The automated Ventana BenchMark immunostainer (Roche, Basel, Switzerland) was used for podoplanin and anti-BRAF V600E staining. Staining was performed according to each protocol. Immunoreactivity was visualized using the Bond Polymer Refine Detection Kit (Leica Biosystems) and the OptiView IHC DAB Kit (Ventana Medical Systems). Tissues were counterstained with hematoxylin II and bluing reagent for 4 minutes. Normal thyroid tissue was used as the negative control for anti-BRAF V600E staining.

5. Statistical analysis

All statistical analyses were performed using SPSS version 28.0 software (IBM Corp., Armonk, NY, USA). Data were compared using the chi-square test, Student *t*-test, and binary logistic regression. Regression analysis was performed to evaluate the risk factors for central LNM and lateral LNM, and the central and lateral LNM groups were compared with the non-metastatic group. Multivariable analysis was performed on meaningful data in the univariable analysis. In all statistical methods implemented, statistical significance was defined as *p*-values of less than 0.05.

Results

1. Clinicopathologic findings

As shown in [Table 1](#), a total of 417 patients with PTC were enrolled. The mean age and median age were 49.66 and 50 years, respectively (range, 15–87 years). Of the total patients, 274 (65.7%) were under the age of 55, and 143 (34.3%) were 55 years of age or older. There were 81 males (19.4%) and 336 females (80.4%). There were 374 and 70 cases with a tumor size smaller than or equal to 10 mm and larger than 10 mm, respectively. One hundred and four cases showed multifocality and 72 cases showed bilaterality. The most common tumor location was in the middle portion (176 cases, 42.2%), followed by the upper pole (122 cases, 29.3%) and the lower pole (104 cases, 24.9%). The classic subtype was the most common with 395 cases (94.7%), and there were 11 cases (2.6%) each of the follicular subtype and other subtypes. The other subtypes included seven cases of tall cell variant, two cases of solid variant, and two cases of oncocytic variant. LNM was observed in 170 cases (40.8%), and LVI and PNI were observed in 33 cases (7.9%) and 22 cases (5.3%), respectively. ETEs were observed in 158 cases (37.9%), and all but one were microscopic extensions. In one case, tracheal invasion was observed at the time of surgery and pathologic confirmation was made. There were 144 (34.5%) cases with lymphocytic thyroiditis. In the immunohistochemical analysis for *BRAF* V600E mutation, 367 cases (88.0%) showed positive findings.

2. Comparison of PTC with or without LNM

There were 170 (40.8%) cases with LNM and 247 (59.2%) cases without LNM. LNM was observed more frequently

Table 1. Clinicopathologic findings in the cohort

Variable	Value (n=417)
Age (yr)	
Mean	49.66
Median (range)	50 (15–87)
<55	274 (65.7)
≥55	143 (34.3)
Sex	
Male	81 (19.4)
Female	336 (80.4)
Tumor size (mm)	
≤10	374 (83.2)
>10	70 (16.8)
Multifocality	
No	313 (75.1)
Yes	104 (24.9)
Bilaterality	
No	345 (82.7)
Yes	72 (17.3)
Location	
Upper	122 (29.3)
Middle	176 (42.2)
Lower	104 (24.9)
Isthmus	11 (2.6)
Entire	4 (1.0)
Subtype	
Classic	395 (94.7)
Follicular	11 (2.6)
Other	11 (2.6)
Lymph node metastasis	
Not identified	247 (59.2)
Present	170 (40.8)
Lymphovascular invasion	
Not identified	384 (92.1)
Present	33 (7.9)
Perineural invasion	
Not identified	395 (94.7)
Present	22 (5.3)
Extrathyroidal extension	
Not identified	259 (62.1)
Present	158 (37.9)
Lymphocytic thyroiditis	
No	273 (65.5)
Yes	144 (34.5)
<i>BRAF</i> V600E mutation	
No	50 (12.0)
Yes	367 (88.0)

Values are presented as number (%) unless otherwise indicated.

and was statistically significant in the following cases: patients under the age of 55 years, male sex, tumor size >10 mm, multifocal tumors, bilateral tumors, tumors involving the lower pole or entire lobe, LVI, PNI, and ETEs (Table 2). There was no significant correlation between tumor subtype, lymphocytic thyroiditis, and *BRAF* V600E mutation with LNM.

3. Central and lateral LNM features

Of the total 170 cases with LNM, 22 (12.9%) spread to the lateral compartment of the neck, while 148 (87.1%) were localized to the central compartment. There was no case of “skip metastasis.” Table 3 shows the differences between the central and lateral LNM groups. The average number of lymph nodes involved with metastatic tumors was significantly different between the lateral LNM group and the central LNM group (9.96±6.56 vs. 2.81±2.27, $p<0.001$). The mean greatest metastatic tumor size was larger in the lateral LNM group (14.18±6.79 mm vs. 3.24±2.80 mm), showing statistical significance ($p<0.001$). An ENE was observed in 17 cases (77.3%) and 45 cases (30.4%) in the lateral and central LNM groups, respectively, and there was a statistically significant difference ($p<0.001$).

4. Risk factors for central LNM

As shown in Table 4, central LNM was correlated with the following factors in the univariable analysis: Age <55 years, male sex, tumor size >10 mm, bilaterality, LVI, and ETEs. However, in the multivariable analysis, age <55 years, male sex, tumor size >10 mm, LVI, and ETEs were associated with central LNM.

5. Risk factors for lateral LNM

Table 5 shows the results of the analysis of the risk factors for lateral LNM. Lateral LNM was correlated with male sex, tumor size >10 mm, multifocality, bilaterality, LVI, PNI, ETEs, and *BRAF* V600E mutation in the univariable analysis. The multivariable analysis showed that male sex, tumor size >10 mm, and LVI were associated with lateral LNM.

6. Risk factors for ENE

The analysis of risk factors for ENE is shown in Table 6. In the univariable analysis, ENEs showed significant associations with tumor size >10 mm, multifocality, bilaterality, PNI, ETEs, and the absence of lymphocytic thyroiditis. The

Table 2. Papillary thyroid carcinoma with and without LNM

Variable	Without LNM (n=247)	With LNM (n=170)	p-value
Age			<0.001
Mean±SD	52.26±11.69	45.46±13.42	
<55 yr	146 (59.1)	128 (75.3)	
≥55 yr	101 (40.9)	42 (24.7)	
Sex			<0.001
Male	30 (12.1)	51 (30.0)	
Female	217 (87.9)	119 (70.0)	
Tumor size			<0.001
Mean±SD	6.53±4.42	10.38±6.95	
≤10 mm	228 (92.3)	119 (70.0)	
>10 mm	19 (7.7)	51 (30.0)	
Multifocality			0.002
No	199 (80.6)	114 (67.1)	
Yes	48 (19.4)	56 (32.9)	
Bilaterality			0.005
No	215 (87.0)	130 (76.5)	
Yes	32 (13.0)	40 (23.5)	
Location			0.024
Upper	77 (31.2)	45 (26.5)	
Middle	112 (45.3)	64 (37.6)	
Lower	49 (19.8)	55 (32.4)	
Isthmus	8 (3.2)	3 (1.8)	
Entire	1 (0.4)	3 (1.8)	
Subtype			0.625
Classic	233 (94.3)	162 (95.3)	
Follicular	6 (2.4)	5 (2.9)	
Other	8 (3.2)	3 (1.8)	
Lymphovascular invasion			<0.001
Not identified	243 (98.4)	141 (82.9)	
Present	4 (1.6)	29 (17.1)	
Perineural invasion			0.025
Not identified	239 (96.8)	156 (91.8)	
Present	8 (3.2)	14 (8.2)	
Extrathyroidal extension			<0.001
Not identified	174 (70.4)	85 (50.0)	
Present	73 (29.6)	85 (50.0)	
Lymphocytic thyroiditis			0.324
No	157 (63.6)	116 (68.2)	
Yes	90 (36.4)	54 (31.2)	
<i>BRAF</i> V600E mutation			0.620
Negative	28 (11.3)	22 (12.9)	
Positive	219 (88.7)	148 (87.1)	

Values are presented as number (%) unless otherwise indicated. LNM, lymph node metastasis; SD, standard deviation.

Table 3. Comparison of central and lateral LNM

	Central LNM (n=148)	Lateral LNM (n=22)	t-value	df ^{a)}	p-value
Average number of dissected lymph nodes	6.74±4.83	29.45±12.66	-15.639	168	<0.001
Average number of involved lymph nodes	2.81±2.27	9.96±6.56	-9.938	168	<0.001
The greatest size of metastatic tumors (mm)	3.24±2.80	14.18±6.79	-13.484	168	<0.001
Extranodal extension					<0.001
Not identified	103 (69.6)	5 (22.7)			
Present	45 (30.4)	17 (77.3)			

Values are presented as mean±standard deviation or number (%).

LNM, lymph node metastasis; df, degrees of freedom.

Table 4. Risk factors for central lymph node metastasis

Factor	Univariable analysis		Multivariable analysis	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (<55/≥55 yr)	0.415 (0.261–0.659)	<0.001	0.351 (0.208–0.591)	<0.001
Sex (M/F)	0.386 (0.228–0.656)	<0.001	0.290 (0.163–0.517)	<0.001
Tumor size (≤10/>10 mm)	4.236 (2.339–7.670)	<0.001	3.628 (1.894–6.950)	<0.001
Multifocality (no/yes)	1.486 (0.885–2.496)	0.134		
Bilaterality (no/yes)	1.928 (1.128–3.297)	0.016	1.215 (0.651–2.268)	0.541
Location				
Upper	Reference			
Middle	1.078 (0.651–1.784)	0.771		
Lower	2.124 (1.128–3.702)	0.008		
Isthmus	0.780 (0.196–3.113)	0.725		
Entire	0.000 (0.000–0.000)	1.000		
Lymphovascular invasion (no/yes)	10.607 (3.577–31.450)	<0.001	8.751 (2.774–27.605)	<0.001
Perineural invasion (no/yes)	2.165 (0.835–5.615)	0.112		
Extrathyroidal extension (no/yes)	2.198 (1.440–3.354)	<0.001	1.897 (1.187–3.031)	0.007
Lymphocytic thyroiditis (no/yes)	0.837 (0.544–1.288)	0.419		
<i>BRAF</i> V600E mutation (no/yes)	1.055 (0.550–2.023)	0.872		

OR, odds ratio; CI, confidence interval; M, male; F, female.

multivariable analysis showed that tumor size >10 mm, multifocality, PNI, ETEs, and the absence of lymphocytic thyroiditis were associated with ENEs.

Discussion

The purpose of this study was to investigate the factors that could predict LNM. Although PTC is known to be an indolent tumor, LNM can occur at an early stage [5]. LNM increases the risk of local recurrence and reoperation and reduces the quality of life [4]. It is common that central LNM precedes lateral LNM, but skip metastasis is also found. Therefore, recognizing the risk factors of LNM and providing appropriate treatment in the initial operation is

important for patient prognosis.

Previous studies showed that factors such as sex, age, ETE, and larger tumor size, especially tumors larger than 10 mm, were associated with LNM [3–5,8]. Kim et al. [9] also showed that the number of tumors was associated with LNM. In this study, LNM was detected in 40.8% of the patients, which was consistent with reports in the literature. LNM was observed at younger ages, in males, in tumor sizes >10 mm, in multiple and bilateral tumors, and in cases with LIV, PNI, and ETEs. In the predictive model, age <55 years, male sex, tumor size larger than 10 mm, LVI, and ETEs were associated with central LNM, and male sex, tumor size >10 mm, and LVI were associated with lateral LNM.

Table 5. Risk factors for lateral lymph node metastasis

Factor	Univariable analysis		Multivariable analysis	
	Crude OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
Age (<55/≥55 yr)	1.011 (0.416–2.454)	0.981		
Sex (M/F)	0.111 (0.044–0.281)	<0.001	0.142 (0.045–0.448)	<0.001
Tumor size (≤10/>10 mm)	14.337 (5.484–37.478)	<0.001	8.279 (2.554–26.841)	<0.001
Multifocality (no/yes)	3.437 (1.402–8.425)	0.007	2.686 (0.846–8.530)	0.094
Bilaterality (no/yes)	3.121 (1.182–8.241)	0.022	1.195 (0.139–10.238)	0.871
Location				
Upper	Reference			
Middle	0.516 (0.172–1.545)	0.237		
Lower	0.982 (0.304–3.175)	0.976		
Isthmus	28.875 (2.679–311.181)	0.006		
Entire	0.000 (0.000–0.000)	0.999		
Lymphovascular invasion (no/yes)	28.233 (7.433–107.242)	<0.001	12.297 (2.554–26.841)	0.002
Perineural invasion (no/yes)	6.611 (1.816–24.073)	0.004	4.734 (0.931–24.058)	0.061
Extrathyroidal extension (no/yes)	4.147 (1.668–10.310)	0.002	1.995 (0.586–6.792)	0.269
Lymphocytic thyroiditis (no/yes)	0.650 (0.246–1.721)	0.386		
<i>BRAF</i> V600E mutation (no/yes)	0.329 (0.119–0.912)	0.033	0.326 (0.094–1.131)	0.077

OR, odds ratio; CI, confidence interval; M, male; F, female.

Table 6. Risk factors for extranodal extension in lymph node metastasis

Factor	Univariable analysis		Multivariable analysis	
	Crude OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
Age (<55/≥55 yr)	1.633 (0.803–3.321)	0.176		
Sex (M/F)	0.528 (0.270–1.033)	0.062		
Tumor size (≤10/>10 mm)	2.700 (1.372–5.312)	0.004	2.332 (1.108–4.906)	0.026
Multifocality (no/yes)	2.636 (1.360–5.112)	0.004	2.288 (1.108–4.728)	0.025
Bilaterality (no/yes)	2.750 (1.331–5.682)	0.006	1.160 (0.316–4.261)	0.823
Location				
Upper	Reference			
Middle	0.467 (0.213–1.023)	0.057		
Lower	0.359 (0.156–0.825)	0.016		
Isthmus	0.478 (0.040–5.658)	0.558		
Entire	1.913 (0.162–22.630)	0.607		
Lymphovascular invasion (no/yes)	1.808 (0.807–4.054)	0.150		
Perineural invasion (no/yes)	5.000 (1.496–16.707)	0.009	4.229 (1.180–15.154)	0.027
Extrathyroidal extension (no/yes)	2.840 (1.481–5.446)	0.002	2.196 (1.085–4.444)	0.029
Lymphocytic thyroiditis (no/yes)	0.377 (0.180–0.790)	0.010	0.414 (0.187–0.915)	0.029
<i>BRAF</i> V600E mutation (no/yes)	1.623 (0.600–4.392)	0.340		

OR, odds ratio; CI, confidence interval; M, male; F, female.

The relationship between tumor location and LNM remains controversial. For tumors located in the upper pole, it has been reported that metastases to the ipsilateral lateral cervical lymph nodes were more common because of the physically close location [4,10]. However, a previous

study found no association between tumor location and LNM [11]. This study showed more frequent LNM in tumors located in the lower pole. However, in the predictive model, tumor location and central and lateral LNM were not correlated.

The follicular type of PTC is known for its less aggressive behavior and better prognosis. The tall cell and solid subtypes are known to be more aggressive and have frequent lymph node metastases. No differences in LNM between subtypes were identified in this study. Most of the cases in this study were the classic type and there were a few cases of other types, so there was a limit to the comparisons that could be made. Whether *BRAF* V600E mutations are related to LNM is still controversial [12-15]. In this study, LNM was not associated with *BRAF* V600E mutations.

This study also revealed that lateral LNM exhibited a more aggressive pattern compared to central LNM, showing a higher number of involved lymph nodes, a larger size of the metastatic tumors, and more frequent ENEs.

ENEs were frequently observed in lateral LNM and were associated with tumor sizes >10 mm, multifocality, PNI, ETes, and the absence of lymphocytic thyroiditis. Multifocality is thought to be associated with more aggressive behavior in PTC [16]. ENEs also seem to be associated with a poor prognosis [17,18]. Zhou et al. [17] reported that patients with ENEs had lower recurrence-free survival rates than patients without ENEs and suggested that ENE was an independent prognostic factor in PTC. Genpeng et al. [18] also showed that ENEs were associated with poor prognosis and proposed a novel staging system that integrated extranodal expansion into the classification of tumors, lymph nodes, and metastases. This study was a retrospective study of the patients who underwent surgery within a short period of 2 years and 10 months, so there was a limit to revealing the relationship between ENEs and the factors predicting prognosis, such as recurrence-free survival. Further investigation on the prognostic relevance of an ENE is needed.

PNI is thought to be invasive in several carcinomas. Rowe et al. [19] showed that nerve density was increased in PTC, and PNI was positively associated with ETes. Although microscopic ETes did not have a significant effect on the prognosis of patients with PTC [20], studies have shown that ENEs were significantly higher in tumors with ETes [21,22]. ENEs were observed to be highly associated with PNI and ETes in this study and these findings are consistent with those of previous studies.

The relationship between lymphocytic thyroiditis and PTC is complex. There is evidence that lymphocytic thyroiditis increases the incidence of PTC [1], but lymphocytic

thyroiditis is also associated with a better prognosis for patients with PTC [23,24]. In this study, ENEs were more frequently observed in the group of patients without lymphocytic thyroiditis. This result supports the results of previous studies on the prognostic relationship between LT and PTC, given the results of this study that ENEs were associated with aggressive factors including PNI and ETes in PTC.

This study has some limitations. First, this study is a retrospective study of the experience of a single institution. Therefore, a sufficient number for each subtype was not included. In addition, due to the lack of sufficient investigation for preoperative examination, the difference between the group with and without preoperative central LNM diagnosis was not compared. Further research will be needed for evaluation of the significance of prophylactic central lymph node dissection.

In summary, the factors predicting central LNM were age <55 years, male sex, tumor size >10 mm, LVI, and ETes. Male sex, tumor size >10 mm, and LVI were considered predictive factors for lateral LNM. ENEs were more frequently observed in lateral LNM, and tumor sizes >10 mm, multifocality, PNI, ETes, and tumors unrelated to lymphocytic thyroiditis were the predictive factors for an ENE. A sufficient preoperative workup for LNM appears to be necessary for younger age groups, males, and tumor sizes larger than 10 mm. If LVI or ETes are observed on pathological evaluation, closer follow-up is required to evaluate local recurrence.

Article information

Conflicts of interest

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

Funding

None.

Author contributions

Conceptualization: JHA, HKC. Data curation: JHA. Formal analysis: JHA. Investigation: JHA. Methodology: JHA, HKC. Project administration: JHA. Resources: JHA. Software: JHA. Supervision: HKC. Validation: JHA. Visualization: JHA. Writing - original draft: JHA. Writing - review & editing: HKC.

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