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Preoperative Factors Associated with Extrathyroidal Extension in Papillary Thyroid Cancer

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Keywords
Extrathyroidal extension · Age · Body mass index · BRAF · Thyroid carcinoma

Abstract
Objective: Extrathyroidal extension may not be accurately recognized during thyroidectomy and can increase the risk of positive margins and even recurrence. This study aimed to investigate the preoperative factors associated with extrathyroidal extension. ***Methods:*** We analyzed 887 patients with papillary thyroid cancer (PTC) who underwent surgery in the period of 2005–2017. Binary logistic regression analyses and generalized additive models were used to identify associations. ***Results:*** Minimal extrathyroidal extension was present in 233 (26%) patients and advanced extrathyroidal extension was found in 60 (7%) patients. Age, BMI, and tumor size were independent predictors of all or advanced extrathyroidal extension. Among the 493 patients whose BRAF mutation status was available, age (OR = 1.025), BMI (OR = 1.091), tumor size (OR = 1.544), and *BRAF* V600E mutation (OR = 2.311) were independently associated with extrathyroidal extension. ***Conclusions:*** Older age, a greater BMI, a larger tumor size, and presence of the *BRAF* mutation were predictive of extrathyroidal extension. These factors should be taken into consideration in decision-making before surgery is performed.

Introduction

Papillary thyroid cancer (PTC) is the most common endocrine malignancy, and its incidence is rising worldwide. Although PTC generally follows an indolent course, an increase in the mortality rate for advanced-stage PTC has been observed [1]. Standard treatment consists of surgery with or without radioactive iodine (RAI) therapy. For patients who have RAI-refractory thyroid cancer, the management options are limited [2]. A few clinicopathologic factors have been identified to be associated with overall survival (OS) in PTC patients [3]. Gender, age, tumor size, extrathyroidal extension, lymph node metastasis, and distant spread are well-known prognostic factors.

Extrathyroidal extension, by definition, is characterized by tumor extension beyond the thyroid capsule into the adjacent soft tissue. It can be subdivided into 2 types,

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i.e., minimal or advanced (extensive). When present, minimal extrathyroidal extension increases the stage of any tumor of <4 cm to the T3 category (according to the 7th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system [AJCC TNM]), and advanced extrathyroidal extension increases it to the T4 category. Nonetheless, the prognostic role of extrathyroidal extension in PTC remains controversial. In the current American Thyroid Association (ATA) guidelines, minimal extrathyroidal extension is considered to indicate an intermediate risk of disease recurrence and/or persistence [4]. On the contrary, in the 8th edition of the AJCC TNM, T3b is defined as a gross extrathyroidal extension invading strap muscles, and minor extension through the thyroid capsule is not included in the staging.

Proper identification of the presence of extrathyroidal extension has some clinical implications. Studies have shown that patients who have extrathyroidal extension are more likely to have positive margins [5, 6]. Accordingly, a more meticulous resection may be required to ensure the completeness of disease eradication. In this study, we aimed to investigate the potential preoperative factors associated with extrathyroidal extension in PTC.

Materials and Methods

Patients

After obtaining institutional review board approval, we queried the prospectively maintained patient registry for all patients undergoing thyroid surgery [7]. We identified patients diagnosed with PTC who underwent an initial surgical treatment with curative intent at our hospital in the period of 2005–2017. Those who were reclassified as having a noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) were not included. Patients younger than 20 years were excluded from this study.

Demographic data including age and gender, as well as body weight and height, were recorded at diagnosis. In Taiwan, overweight and obesity are defined as a BMI ≥24 and ≥27, respectively, because Asians have a higher rate of comorbidity and fat mass at lower BMI levels than Caucasians do [8].

Preoperative Workup

A preoperative neck ultrasound was performed by endocrinologists and/or endocrine surgeons [9, 10]. For each thyroid nodule, tumor diameters were measured on the anteroposterior, transverse, and longitudinal planes. Tumor size was defined as the greatest diameter of each lesion. The diagnosis of Hashimoto's thyroiditis was made based on the characteristic ultrasound pattern of the thyroid parenchyma in conjunction with positive serum autoantibodies against thyroid peroxidase and/or thyroglobulin. The *BRAF* V600E mutation status was determined by Sanger sequencing on cytological cell blocks or surgical specimens [11, 12]. The *BRAF* mutation was for tested selectively before 2015 and routinely after 2015.

Extrathyroidal Extension

During the study period, a total thyroidectomy was performed for differentiated thyroid cancer >1 cm, and lobectomy was done for microcarcinoma [13]. Nonetheless, the operative procedure was finally determined after sharing the decision-making with the patient. All microscopic slides and pathology reports were reviewed by 2 pathologists [14].

The 7th edition of the AJCC TNM criteria was implemented at our institute until the end of 2017. Accordingly, minimal extrathyroidal extension (T3) is characterized by involvement of the sternothyroid muscle or perithyroidal soft tissues and it is generally identified by light microscopic examination. Advanced extrathyroidal extension (T4) is defined as direct extension of the tumor into the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve. No patient in our series had very advanced disease, in which the cancer invades the prevertebral fascia or encases the carotid artery or mediastinal vessels.

Statistical Analysis

Continuous variables were tested for normality using the D'Agostino-Pearson omnibus K2 normality test. As transformations did not improve normality, nonparametric tests were used throughout. Data are expressed as medians (IQR) or numbers (%). We treated extrathyroidal extension as an ordered categorical variable. The Cochran-Armitage trend test was used to examine associations with dichotomous parameters, and the Jonckheere-Terpstra test was used for continuous variables [15]. To explore possible associations with BMI, we used the Mann-Whitney U test for dichotomous parameters and the Spearman rank correlation coefficient for continuous variables.

Binary logistic regression analysis was performed to identify preoperative determinants of extrathyroidal extension [16]. Predictors with $p < 0.05$ in the univariate logistic regression analysis were included in multivariate models. OR and 95% CI are reported. We evaluated the performance of the models by calculating the area under the receiver operating characteristic (ROC) curve and the goodness of fit by means of the Hosmer-Lemeshow test. To relax the linearity assumptions, generalized additive models were also plotted and adjusted for appropriate covariates [17].

The secondary analysis incorporated the *BRAF* mutation status. For visual assessment of the association between BMI and the *BRAF* mutation, the relationships were fitted using a nonparametric regression method, i.e., locally weighted scatterplot smoothing (LOWESS). The LOWESS regression method does not require any a priori known relationship between the predictor and the dependent variables [18]. Furthermore, we used multiple imputation to account for missing information in cases with an unknown *BRAF* mutation status. To redeem the bias of different *BRAF* test policies, a missing *BRAF* mutation status was imputed using the year of diagnosis. The final imputed dataset was assessed as a sensitivity analysis.

All analyses were performed with Stata v14.0 software (StataCorp., College Station, TX, USA). A two-sided $p < 0.05$ was considered statistically significant.

Table 1. Associations between preoperative parameters and extrathyroidal extension in patients with PTC

Variable	Extrathyroidal extension			*p* value
	none (*n* = 594)	minimal (*n* = 233)	advanced (*n* = 60)	
Age	45 (36–54)	48 (39–57)	55 (45–62)	<0.001
Female sex	497 (84)	184 (79)	47 (78)	0.094
BMI	23.2 (21.1–25.6)	23.8 (21.9–27.8)	25.4 (22.7–28.4)	<0.001
Category				<0.001
Underweight	25 (4)	8 (3)	1 (2)	
Normal	325 (55)	112 (48)	18 (30)	
Overweight	144 (24)	47 (20)	19 (32)	
Obese	100 (17)	66 (28)	22 (37)	
Tumor size	1.2 (0.7–2.0)	1.9 (1.3–2.5)	2.9 (2.2–3.5)	<0.001
Hashimoto's thyroiditis	91 (15)	45 (19)	4 (7)	0.683
BRAF mutation[a]	196 (67)	130 (81)	38 (93)	<0.001

Values are presented as medians (IQR) or numbers (%).The total number is patients is 887. [a] Status was available for 493 patients.

Table 2. Univariate and multivariate logistic regression analysis of factors associated with extrathyroidal extension in patients with PTC

Variable	Extrathyroidal extension (all)						Advanced extrathyroidal extension (T4 stage)					
	univariate			multivariate			univariate			multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.025	1.014–1.037	<0.001	1.031	1.019–1.044	<0.001	1.042	1.022–1.063	<0.001	1.046	1.025–1.067	<0.001
Sex	0.727	0.510–1.037	0.078				0.775	0.409–1.469	0.435			
BMI	1.094	1.055–1.135	<0.001	1.074	1.032–1.117	<0.001	1.114	1.050–1.183	<0.001	1.081	1.010–1.156	0.024
Tumor size	1.758	1.545–2.001	<0.001	1.847	1.614–2.114	<0.001	1.915	1.588–2.309	<0.001	2.052	1.668–2.523	<0.001
Hashimoto's thyroiditis	1.110	0.760–1.622	0.590				0.363	0.129–1.017	0.054			

The total number of patients was 887.

Results

A total of 887 patients with PTC met the inclusion criteria. About 80% (*n* = 728) were women. The median age at diagnosis was 47 years (range 20–91). The median BMI was 23.6 (range 16.4–43.0), with 34 patients (4%) being underweight, 455 (51%) being within the normal range, 210 (24%) being overweight, and 188 (21%) being obese. Of these patients, 703 (79%) underwent a total thyroidectomy and 184 (21%) had a lobectomy. The median tumor size was 1.5 cm, and 262 tumors (30%) were microcarcinomas. Concurrent Hashimoto's thyroiditis was present in 140 (16%) patients.

Based on clinical features and pathologic examination, 594 (67%) patients had no extrathyroidal extension, 233 (26%) presented with minimal extrathyroidal extension, and 60 (7%) had advanced extrathyroidal extension. As shown in Table 1, extrathyroidal extension in PTC was associated with an older age, a greater BMI, and a larger tumor size. Interestingly, the prevalence of overweight and obesity was 41, 48, and 68% in patients with no, minimal, and advanced extrathyroidal extension, respectively. BMI was positively associated with age (Spearman's $\rho = 0.201$, $p < 0.001$), and men had significantly higher BMI than women (median 24.6 vs. 23.2, $p < 0.001$). BMI was not associated with tumor size or Hashimoto's thyroiditis.

Next, we employed logistic regression to model the probability of extrathyroidal extension based on these preoperative factors. Consistently, age, BMI, and tumor size were independent predictors of extrathyroidal extension in PTC (Table 2). The area under the ROC curve was 0.741 (95% CI 0.707–0.775) with a good fit (Hosmer-Lemeshow test, $p = 0.240$). Additionally, OR were estimated using generalized additive models. Of interest, the OR for extrathyroidal extension increased in a nearly linear fashion along with increasing patient age or BMI (Fig. 1). An inverted U-shaped relationship was found for tumor size after adjustment for age, sex, and BMI.

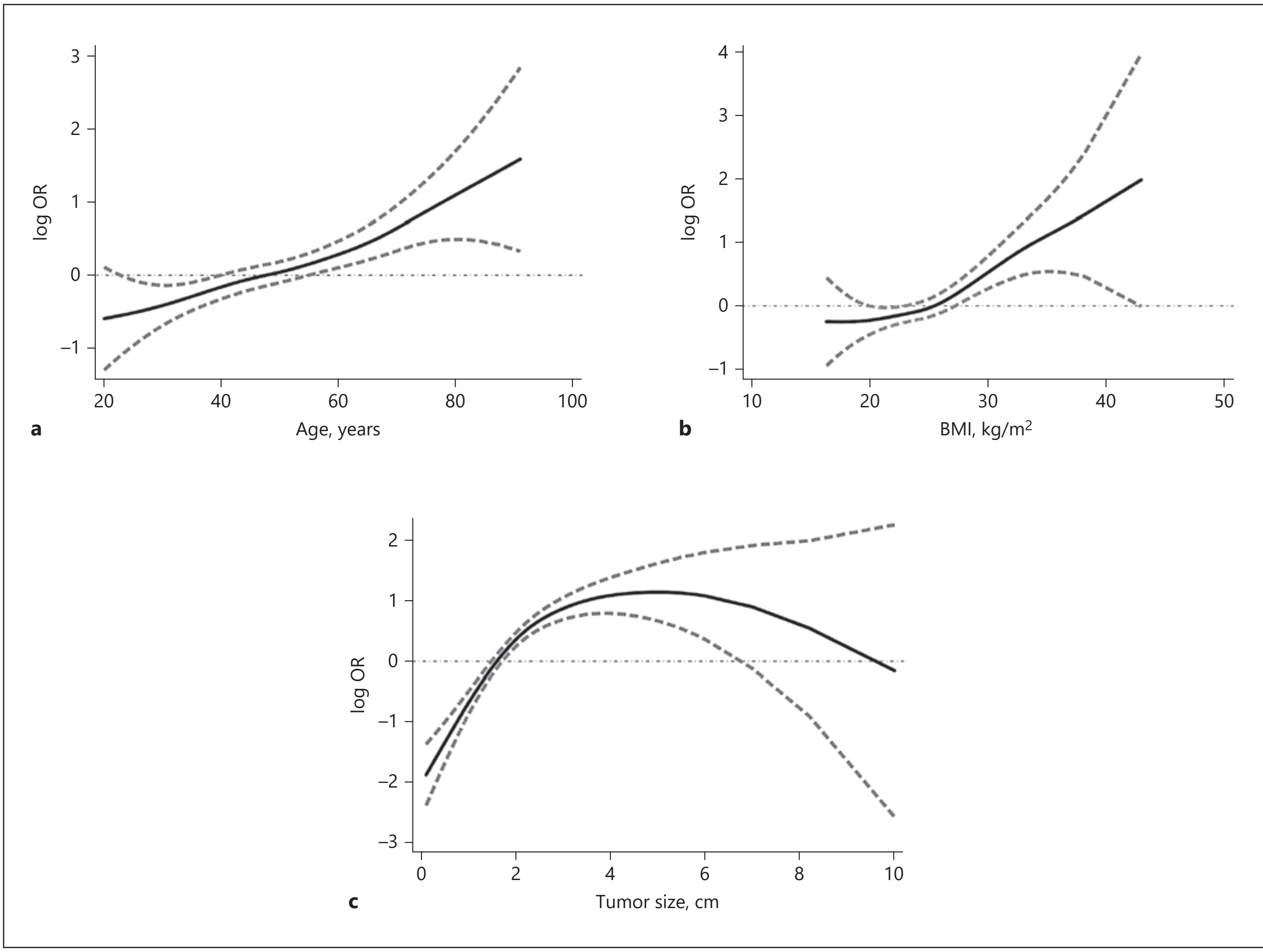

Fig. 1. Log-transformed OR and 95% CI (dashed lines) for extrathyroidal extension at a given age (**a**), BMI (**b**), or tumor diameter (**c**) in 887 patients with PTC. Estimates were obtained from generalized additive models adjusted for sex (**a**), sex and age (**b**), and sex, age, and BMI (**c**), respectively.

We further analyzed the potential factors associated with advanced extrathyroidal extension. In agreement with a previous analysis, age (OR = 1.046), BMI (OR = 1.081), and tumor size (OR = 2.052) were independently associated with advanced extrathyroidal extension (Table 2). The area under the ROC curve was 0.835 (95% CI 0.787–0.884). The model was well fitted (Hosmer-Lemeshow test, $p = 0.483$).

BRAF mutation status data were available for 493 patients (56%); 364 (74%) carried the *BRAF* V600E mutation. The presence of the *BRAF* mutation was associated with an older age ($p = 0.002$) and a higher BMI ($p = 0.015$) but not with gender or tumor size. We further explored the association between BMI and the *BRAF* mutation by modeling the relationship using a LOWESS plot (Fig. 2). The plot suggested that increasing BMI did indeed correlate with a higher prevalence of the *BRAF* mutation in PTC.

Given that it is possible to obtain the *BRAF* mutation status by fine-needle aspiration biopsy of thyroid nodules, we performed a secondary analysis that incorporated the *BRAF* mutation status. As shown in Table 3, age (OR = 1.025), BMI (OR = 1.091), tumor size (OR = 1.544), and *BRAF* mutation (OR = 2.311) were independent predictors of extrathyroidal extension in PTC. The area under the ROC curve was 0.714 (95% CI 0.667–0.760). The model overall fits the data well (Hosmer-Lemeshow test, $p = 0.313$).

The *BRAF* mutation was tested for selectively before 2015. To account for the possibility that only the more

Table 3. Univariate and multivariate logistic regression analysis of factors (incorporating the status of BRAF mutation) associated with extrathyroidal extension in patients with PTC

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.026	1.012–1.040	<0.001	1.025	1.009–1.040	0.002
Sex	0.792	0.498–1.260	0.325			
Body mass index	1.115	1.064–1.169	<0.001	1.091	1.038–1.147	0.001
Tumor size	1.457	1.236–1.717	<0.001	1.544	1.291–1.846	<0.001
Hashimoto's thyroiditis	0.788	0.502–1.237	0.300			
BRAF mutation	2.494	1.596–3.895	<0.001	2.311	1.438–3.713	0.001

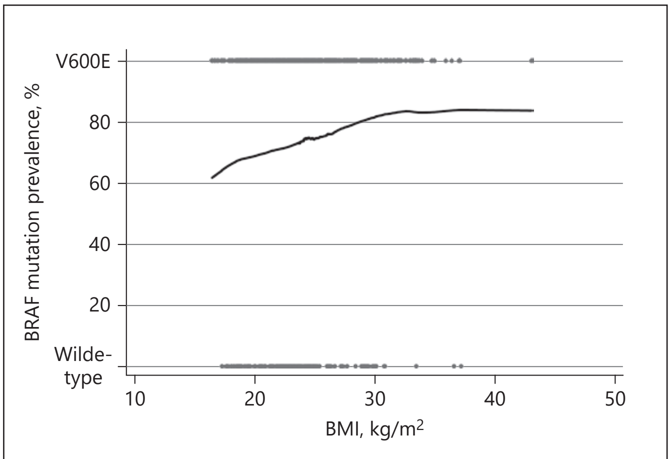

Fig. 2. Plot depicting the relationship between BMI and the status of BRAF mutation in 493 patients with PTC. The trend is shown by the LOWESS line. Degree of smoothing = 0.9.

aggressive tumors were tested for, iterative rounds of imputation (n = 20) were performed to impute the *BRAF* mutation status based on the year of diagnosis. The results from the sensitivity analysis using multiple imputation showed no remarkable difference (Table 4). This indicates that, where data were missing, this did not cause any considerable bias in the estimation of regression coefficients.

Table 4. Multivariate logistic regression analysis of factors associated with extrathyroidal extension after multiple imputation of missing data on the status of BRAF mutation in patients with PTC

Variable	OR	95% CI	*p* value
Age	1.030	1.017–1.043	<0.001
BMI	1.070	1.029–1.114	0.001
Tumor size	1.862	1.623–2.136	<0.001
BRAF mutation	1.820	1.144–2.896	0.012

Discussion

It is generally accepted that advanced extrathyroidal extension negatively impacts outcomes in PTC. The 2015 ATA guidelines classified macroscopic invasion into the perithyroidal soft tissues as high-risk disease and recommended a near-total or total thyroidectomy with RAI adjuvant therapy in patients with gross extrathyroidal extension [4]. Likewise, RAI adjuvant therapy should be considered after a total thyroidectomy in intermediate-risk patients who have minimal extrathyroidal extension. Despite controversy, tumors with minimal extrathyroidal extension might have a higher recurrence rate than those with no extrathyroidal extension [19–21]. An analysis of the National Cancer Database demonstrated that even a minimal extrathyroidal extension was associated with a compromised overall survival [22]. Interestingly, our findings suggest that minimal and advanced extrathyroidal extension have similar associations with some of the preoperative factors.

Although extrathyroidal extension bears some prognostic significance, intraoperative inspection for extrathyroidal extension is often inaccurate [23]. Intraoperative frozen sections may be helpful to identify the presence of extrathyroidal extension [24], but the number of frozen sections has dramatically decreased in recent years. Preoperative neck ultrasound plays a pivotal role in characterization and staging of thyroid nodules. Common sonographic features of extrathyroidal extension include a thyroid capsular distortion or abutment, contour bulging, a long interface between the tumor and the thyroid capsule, and a tracheal footprint. It is not difficult to discern advanced extrathyroidal extension on ultrasound. Nonetheless, the positive predictive value of predicting minimal extrathyroidal extension is modest [25, 26]. In this context, proper identification of associated factors may alert physicians to the presence of extrathyroidal extension.

We found that *BRAF* mutation, tumor size, BMI, and age were independent predictive factors. Of these factors, *BRAF* mutation is the most common oncogenic driver of PTC but there are wide global variations in the occurrence rate. *BRAF* mutation analysis has a high rule-in capacity in cytologically indeterminate thyroid nodules. Additionally, previous studies have established a positive association between the *BRAF* V600E mutation and most of the clinical features of aggressiveness, including extrathyroidal extension, lymph node metastasis, and an advanced stage [11, 27]. Nonetheless, this information is not always available before surgery.

Consistent with a previous report [28], we found that tumor size was an independent risk factor for extrathyroidal extension. This is comprehensible because continuous tumor growth would lead to a higher likelihood of extension beyond the thyroid capsule, particularly in those tumors in the periphery. An older age was also independently associated with extrathyroidal extension. We previously reported that an older age was associated with a glycolytic phenotype of PTC [29]. Local acidification of the tumor microenvironment in association with the Warburg effect may potentially support tumor invasion [30]. Furthermore, aging restrains adaptive immunity and renders the tumor microenvironment more immunosuppressive, which may facilitate the invasion process [31].

An intriguing finding in this study is that a higher BMI of patients was modestly but independently associated with extrathyroidal extension. Overweight and obesity are associated with a higher risk of the occurrence of thyroid cancer [32]. Additionally, obese patients with PTC have an increased risk of developing locoregional events during follow-up [33]. In a large Korean series, higher BMI could predict multiplicity and extrathyroidal extension, whereas a higher body surface area was a predictor for multiplicity [34]. Possible mechanisms involving the link between adiposity and cancer include insulin resistance, adipokine, and subclinical inflammation. We have demonstrated that leptin and adiponectin receptors are present in PTC and have correlations with some clinicopathologic features [35–37]. Recently, Pitoia et al. [38] found that the state of insulin resistance was associated with structural persistent disease. It is noteworthy that we observed a positive association between BMI and BRAF V600E mutation. These findings are in line with an early study [39]. Further research is necessary to elucidate the mechanisms underlying the link between obesity and BRAF mutation.

In conclusion, age, BMI, tumor size, and BRAF mutation are preoperative factors associated with extrathyroidal extension in PTC. Although BMI is typically not considered a prognostic variable, it is the only modifiable risk factor. It would be of great interest to know whether weight reduction is helpful in terms of long-term outcomes in obese patients with PTC.

Statement of Ethics

This study was approved by the Institutional Review Board of the MacKay Memorial Hospital. All of the procedures involving human participants were in accordance with the ethics standards of the MacKay Memorial Hospital and the 1964 Helsinki Declaration and its later amendments or comparable standards. For this type of study, formal consent is waived.

Disclosure Statement

The authors have no conflict of interests to declare.

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Author Contributions

Study conception and design: C.-Y.K., P.-S.Y., and S.-P.C. Acquisition of data: C.-Y.K. and S.-P.C. Analysis and interpretation of data: C.-Y.K., P.-S.Y., M.-N.C., and S.-P.C. Drafting of this paper: C.-Y.K. and S.-P.C. Critical revision: P.-S.Y. and M.-N.C. All of the authors read and approved the final version of this paper.

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