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ORIGINAL ARTICLE

Ultrasound combined with biochemical parameters can predict parathyroid carcinoma in patients with primary hyperparathyroidism

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Abstract

Purposes Parathyroid cancer (PC) is rare, but fatal condition. Preoperative prediction of PC remains challenging but meaningful. The aim of this study was to determine an effective model to predict PC in patients with parathyroid lesions >1.5 cm.

Methods In this retrospective case-control study, we enrolled 30 patients with PC matched to 60 patients with parathyroid adenoma or hyperplasia by admission year. All patients were diagnosed with primary hyperparathyroidism (pHPT) and had parathyroid lesions >1.5 cm. Ultrasonic features of the two patient groups, as well as demographic, clinical, and biochemical characteristics were retrospectively compared. Best subset selection and multivariate logistic regression analysis were conducted to identify the independent risk factors of PC. ROC curve and decision curve analysis were developed to evaluate the applicability of the new model.

Results The best subset selection method and multiple logistic regression analysis showed that ultrasonic features of DR (two diameters' ratio of the lesion) and tumor infiltration in conjunction with intact parathyroid hormone (iPTH) level (collective model) were independent predictors of malignancy. Meanwhile, DR, shape, and tumor infiltration (ultrasound model) were found to be risk factors when only ultrasonic features were included in the multivariate analysis. The decision curve analysis showed that collective model outperforms ultrasound model with a better net benefit and a wider range of threshold probabilities.

Conclusions Ultrasonic features in combination with iPTH level may be an applicable model for predicting PC and has a better potential to facilitate decision-making preoperatively.

Keywords Parathyroid carcinoma · Ultrasonography · Diagnosis · Primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (pHPT) is one of the most common endocrine disorders that predominantly affects women [1]. Solitary adenoma attributes to 80–90% pHPT. Cancer is rare and occurs in less than 1% of patients with pHPT as reported in some western countries, while its incidence in China was reported above 5% in pHPT [2, 3]. Although displaying as a rare entity, parathyroid carcinoma means totally different management and outcome. About 60% patients with parathyroid cancer (PC) suffered from repeated recurrence or metastasis, and the main reason for mortality was uncontrollable hypercalcemia rather than the invasion of tumor [4]. Instead of local parathyroidectomy, radical resection of lesion with surrounding tissue was required for PC in the initial operation. Early and accurate

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diagnosis of parathyroid carcinoma can reduce morbidity and mortality. ^{99m}Tc sestamibi (MIBI) scanning is good at detecting the locations of parathyroid masses, but it is difficult for sestamibi scintigraphy to provide more detail about the lesion. In contrast, ultrasound allows observation of the nodule from many angles thereby providing information of intratumoral structure. And this convenient and inexpensive modality, as a method of choice in our study, can evaluate the parathyroid gland with great sensitivity and specificity [5]. Owing to the rarity of PC, there are no effective diagnostic markers in clinical situation so far and its ultrasound imaging features have not yet fully investigated. The definitive diagnosis of parathyroid malignancy is based on the following clinicopathological features set out by World Health Organization 2017 criteria: definite tumor invasion to neighboring anatomic structures, vascular invasion, perineural invasion, and metastasis [6]. However, considering that minimally invasive surgery have gradually become mainstay treatments for parathyroid adenoma due to numerous benefits, it is quite important to recognize PC prior to surgery for that radical resection is needed for malignancy.

Several studies have focused on the preoperative diagnosis of PC, while the disparity in demographic characteristics, sample sizes, and baseline variables limited the clinical application of findings in these literature. Furthermore, most previous studies focused only on either clinical parameters or the ultrasound characteristics. A predictive model combined with clinical features, biochemical results, and ultrasound information may facilitate decision-making for PC before operation. Herein, we aimed to explore an effective model of identifying parathyroid carcinoma preoperatively. As the malignancy is rarely <1.5 cm in size according to our data and previous reports [3], this study aimed to explore the ultrasonographic and biochemical features that can predict parathyroid carcinoma in tumors with sizes >1.5 cm.

Subjects and methods

Patients and clinical data

This hospital-based case-control study was approved by Ethics Committee of Peking Union Medical College Hospital and written consent was obtained from all patients to use their data for research purpose. From January 2000 to December 2018, a total of 65 patients were diagnosed with PC based on pathological examination with WHO classification in the Peking Union Medical College Hospital. Among them, 35 patients were finally excluded from the present study. The exclusion criteria were: secondary or tertiary hyperparathyroidism, multiple gland disease, familial syndromes (MEN1, MEN2A, and hyperparathyroidism-jaw tumor syndrome), underwent US scan or primary surgery at other institutions, and incomplete medical records. Sixty patients with pHPT with benign lesions and size >1.5 cm were enrolled as control group, who were admitted in the same period as PC patients. Patients were ruled out provided they matched exclusion criterion all above. When more than two controls for each case of parathyroid carcinoma were matched, we selected controls by looking up random number table. Finally, the enrolled 60 patients in control group included 3 parathyroid hyperplasia, 50 adenoma, and 7 atypical adenoma. Overall, 90 patients with complete preoperative patient records and histopathology results were enrolled in the study.

Demographic, clinical, and biochemical data were collected retrospectively. Biochemical data included preoperative intact parathyroid hormone (iPTH, range 12–68 pg/mL), serum calcium (Ca, range 2.13–2.70 mmol/L), phosphorus (P, range 0.81–1.45 mmol/L), and alkaline phosphatase (ALP, range 35–100 IU/L) levels. Siemens Immulite 2000 and Beckman DxI800 platforms were employed to determine iPTH level using the second-generation assay technique. The maximum value of biochemical parameters before surgery was used for analysis. Symptoms were classified into three categories based on duration and severity of the disease. Grade 0 represented no overt symptoms reported and the tumor was accidentally discovered. Grade 1 represented classical symptoms that lasted less than a year involving one or more of the following systems: skeleton, kidney, neuromuscular system, gastrointestinal tract, cardiovascular system, and neurocognitive features. Grade 2 represented symptoms that lasted more than a year, obvious signs or quickly worsening symptoms that required hospitalization, including but not limited to palpable neck mass, osteitis fibrosa cystica, fractures, pancreatitis, intractable vomiting, and hypercalcemic crisis.

Ultrasonography examination

All the patients underwent preoperative ultrasonic examinations to identify and characterize the lesions by ultrasonographic specialists with over 5 years of experience. HDI 5000 7–15-MHz linear probe (Philips Medical Systems, Bothell, WA) or iU22 5–12-MHz linear probe was used for ultrasonography. Patients were put in supine position with an extended neck during examination. A junior resident doctor accessed the archives and retrieved pictures from the medical records or imaging storage system. Two senior resident doctors who were blinded to histopathological findings evaluated the US features of the lesions according to a pre-agreed protocol. The consensus was made after a discussion among the two senior residents and a specialist with over 20 years' experience in thyroid and parathyroid imaging. When multiple lesions were identified by ultrasound, only those that were confirmed pathologically and excised were taken into consideration and patients with more than one lesion intraoperatively were excluded from the study. Classification criteria for the parathyroid lesions were as follows: location (right, left, or ectopic), size, diameter ratio (DR), shape (oval/round or irregular), echogenicity, calcification, cystic change, and infiltration. Size was defined as the maximum diameter of lesions on US imaging. DR was the ratio between the lesion's maximum diameter and minimum diameter, which were measured by the initial observer in two planes. Operationally, after adjustment of ultrasound probe to identify the size of lesion in different planes, the maximum diameter of parathyroid mass was measured in a plane, usually the longitudinal plane, while the minimum diameter was often determined in short-axis plane, which could be the depth or width of the lesion. Lesions were recorded as homogeneous, heterogeneous, and mixed echogenicity based on their ultrasonographic appearance (Fig. 1). Calcification and cystic change referred to high reflective foci with or without acoustic shadowing and anechoic area clearly detected, respectively. Infiltration was considered when abnormal tissue extended beyond the perceived smooth outline, thereby completely or partially obscuring the echogenic rim of the lesion.

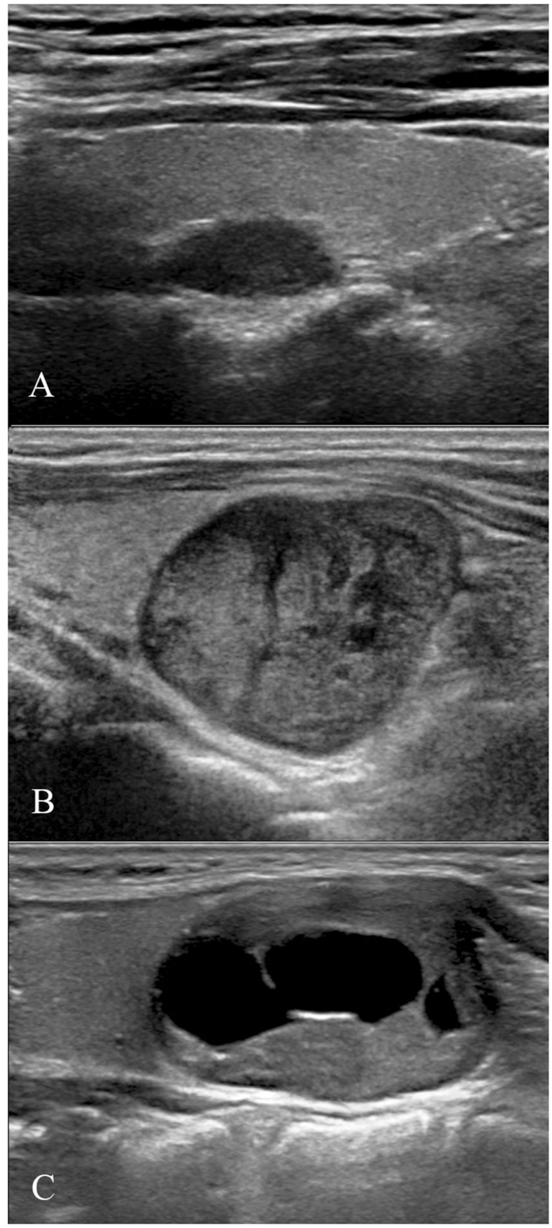

Fig. 1 The typical ultrasound presentation of parathyroid neoplasm. **a** Homogeneous hypoechoic reflectivity with oval shape of a typical parathyroid adenoma; **b** heterogeneous appearance of a parathyroid carcinoma; **c** mixed echotexture with cyst change of an atypical adenoma

Statistics

Data analysis was performed using STATA 15.0 (Stata Corporation, College Station, TX, USA), R 3.5.2 (R Foundation for Statistical Computing, www.R-project.org). The normality of variables was verified using a Kolmogorov–Smirnov test. Biochemical parameters were shown as the median and interquartile range and comparison between the two groups were conducted using Mann–Whitney U test. Age of patients and diameters of the US features were compared by independent samples Student's *t* test and shown as the mean ± standard deviation. Meanwhile, categorical variables were evaluated using the chi-square test or Fisher's exact test and were shown as the number of individuals and percentages. Symptom grades of two groups were evaluated by Cochran–Armitage test for trend. Any variables that were clinically significant or that showed a univariate relationship with the outcome were included in the multivariate analysis. Given the number of cases available, we performed best subset selection in accordance with Bayesian information criterion to determine more relevant factors. Best subset selection method can reach the optimum combination from available variables. Binary logistic regression model was used to assess these factors. The receiver operating characteristic (ROC) curve was constructed and area under the curve (AUC) was estimated to evaluate related variables and final model. The optimal cutoff point was identified for continuous variables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The results were presented as the odds ratios with 95% confidence interval (CI), Wald statistics, and *p*-value. Meanwhile, decision curve analysis for the case-control study was performed for comparing clinical applicability of different models. The true prevalence of parathyroid carcinoma was presumed as 0.01 based on previous studies. A statistical significance was considered if a p-value was below 0.05.

Results

Ninety patients with pHPT were enrolled in this study. Overall, 57 (63.3%) patients were female, 33 (36.7%) patients were male, and the mean age was 52.4 ± 13.0 years. No significant difference in age was observed between the malignant and benign groups ($p = 0.091$), but a gender preponderance was found between them ($p = 0.005$). There were more females in PA group and more males in PC group. Serum iPTH, Ca, and ALP levels were markedly higher in PC group compared with PA group ($p < 0.0005$, $p = 0.001$, and $p < 0.0005$, respectively). Serum P level was significantly lower in PC group relative to PA ($p < 0.0005$). By Cochrane-Armitage test, PC presented with more severe symptoms compared with PA ($p < 0.0005$) (Table 1).

The sonographic features of these lesions were shown in Table 1. Size (the maximum diameter of lesion) was significantly different between the two groups. As expected, the size of parathyroid carcinoma was larger than that of adenoma or hyperplasia ($p = 0.03$). Moreover, the DR of PC group was significantly lower than that of benign group ($p < 0.0005$). The location of the tumor was not different between the two groups ($p = 0.053$). In contrast, irregular shape was more prevalent in the PC group than in the PA group ($p < 0.0005$). With regard to echogenicity, heterogeneous mass was more frequent than homogeneous nodules in PC group ($p < 0.0005$). Calcification and infiltration were highly prevalent in the parathyroid carcinomas ($p = 0.003$ and $p < 0.0005$, respectively). Intra-lesion cystic change was present in 19 (31.7%) benign lesions and 14 (46.7%) parathyroid carcinoma cases, and no significant difference was found between the two groups ($p = 0.164$) (Fig. 2).

For diagnosis of PC, the AUC for serum iPTH was 0.836 (95% CI: 0.740–0.931, $p < 0.0005$). The best cutoff value of iPTH in predicting cancer was 509 pg/mL (sensitivity: 76.7%, specificity: 88.3%, PPV: 76.7%, NPV: 88.3%). The AUC for serum ALP was 0.907 (95% CI: 0.846–0.967, $p < 0.0005$) and the best cutoff value for ALP was 152 IU/L (sensitivity: 93.3%, specificity: 78.3%, PPV: 68.3%, NPV: 95.9%). As to ultrasound features, the best cutoff value for lesion size and DR were 2.05 cm (sensitivity: 96.7%, specificity: 43.3%, PPV: 46.0%, NPV: 96.3%) and 1.86 (sensitivity: 70.0%, specificity: 91.7%, PPV: 80.8%, NPV: 85.9%), respectively. The infiltration appearance in sonogram showed relatively better diagnostic accuracy as well (AUC = 0.842, 95% CI: 0.743–0.940, $p < 0.0005$) (Table 2).

Table 1 Comparison of demographic, clinical, and ultrasound parameters between parathyroid benign lesions (parathyroid adenoma/hyperplasia) and carcinomas

	Parathyroid adenoma/ hyperplasia ($n = 60$)	Parathyroid carcinoma ($n = 30$)	p-value
Mean age (years)	54.1 ± 13.0	49.2 ± 12.6	0.091
Gender (male/female)	16/44	17/13	0.005
Serum iPTH (pg/mL)	207.1 (144.9–333.8)	1085.5 (523.8–1565.5)	<0.001
Serum Ca (mmol/L)	2.79 (2.72–2.99)	3.20 (2.89–3.57)	0.001
Serum P (mmol/L)	0.82 (0.66–0.93)	0.58 (0.54–0.75)	<0.001
Serum ALP (IU/L)	108.5 (77.5–142.3)	414.5 (204.8–682.5)	<0.001
Symptoms			<0.001
0	27 (87.1%)	4 (12.9%)	
1	17 (73.9%)	6 (26.1%)	
2	16 (44.4%)	20 (55.6%)	
Size (cm)	2.61 ± 1.20	3.20 ± 1.11	0.03
DR	2.69 ± 0.88	1.83 ± 0.74	<0.001
Location			0.053
Right	35 (58.3%)	10(33.3%)	
Left	21 (35.0%)	18(60.0%)	
Ectopic	4 (6.7%)	2(6.7%)	
Shape			<0.001
Oval/round	37 (61.7%)	6 (20.0%)	
Irregular	23 (38.3%)	24 (80.0%)	
Echogenicity			<0.001
Homogeneous	36 (60.0%)	6 (20.0%)	
Heterogeneous	24 (40%)	24 (80%)	
Calcification	5 (8.3%)	10 (33.3%)	0.003
Cystic change	19 (31.7%)	14 (46.7%)	0.164
Infiltration	5 (8.3%)	23 (76.7%)	<0.001

Ca calcium, *iPTH* intact parathyroid hormone, *ALP* alkaline phosphatase, *P* phosphatase

Univariate analysis and subsequent best subset selection method (Fig. 3a) were performed to identify the potential risk factors of parathyroid carcinoma. Variables that were found to be statistically relevant based on univariate analysis and best subset selection or showing clinical relevance were included in the multiple logistic regression analysis. A collective model including serum iPTH level, ultrasound findings of DR, and infiltration could predict malignancy with a AUC of 0.96. Meanwhile, a second model was established using ultrasonographic features, and its AUC in predicting PC was 0.94 (Fig. 3b). It was found that shape, infiltration, and DR were independent risk factors according to multivariate analysis in the ultrasound model. Two models showed no statistical significance concerning AUC ($p = 0.4947$). In collective model, the risk of malignance increased by 1.185-fold for every 100 pg/mL of serum iPTH (95% CI: 1.047–1.341, $p = 0.007$). The OR of the tumor infiltration on ultrasonography for malignancy was 45.037 (95% CI: 8.633–234.968, $p < 0.0005$). On the other hand, the risk of parathyroid malignancy was 4.098-fold lower with one additional DR value (95% CI: 1.362–12.346, $p = 0.012$). In ultrasound model, comprising of ultrasonic features alone, we found that the risk factors of parathyroid carcinoma were DR (OR 6.135, 95%

Table 2 Areas under curve, best cutoff points, and diagnostic performance for biochemical and ultrasonographic parameters in differentiating between the parathyroid adenoma and carcinoma

	AUC	95% CI	Cutoff value	*p*-value	Sensitivity	Specificity	PPV	NPV
Biochemical parameters								
Serum Ca (mmol/L)	0.723	0.602–0.844	>2.88	0.001	0.767	0.667	0.537	0.837
Serum iPTH (pg/mL)	0.836	0.740–0.931	>509	<0.001	0.767	0.883	0.767	0.883
Serum ALP (IU/L)	0.907	0.846–0.967	>152	<0.001	0.933	0.783	0.683	0.959
Serum P (mmol/L)	0.732	0.612–0.852	<0.64	<0.001	0.633	0.817	0.633	0.817
Ultrasound features								
Size	0.690	0.579–0.800	>2.05	0.003	0.967	0.433	0.460	0.963
DR	0.839	0.741–0.936	<1.86	<0.001	0.700	0.917	0.808	0.859
Irregular shape	0.708	0.596–0.820		0.001	0.800	0.383	0.512	0.860
Heterogeneous	0.700	0.587–0.813		0.002	0.800	0.600	0.500	0.857
Infiltration	0.842	0.743–0.940		<0.001	0.767	0.917	0.821	0.887
Calcification	0.625	0.496–0.754		0.054	0.333	0.917	0.667	0.733
Cystic	0.575	0.448–0.702		0.248	0.467	0.683	0.424	0.719
Collective model	0.956	0.919–0.992		<0.001	0.800	0.912	0.828	0.902
Ultrasound model	0.942	0.891–0.993		<0.001	0.800	0.933	0.857	0.903

Ca calcium, *iPTH* intact parathyroid hormone, *ALP* alkaline phosphatase, *P* phosphatase, *AUC* area under curve, 95% *CI* 95% confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

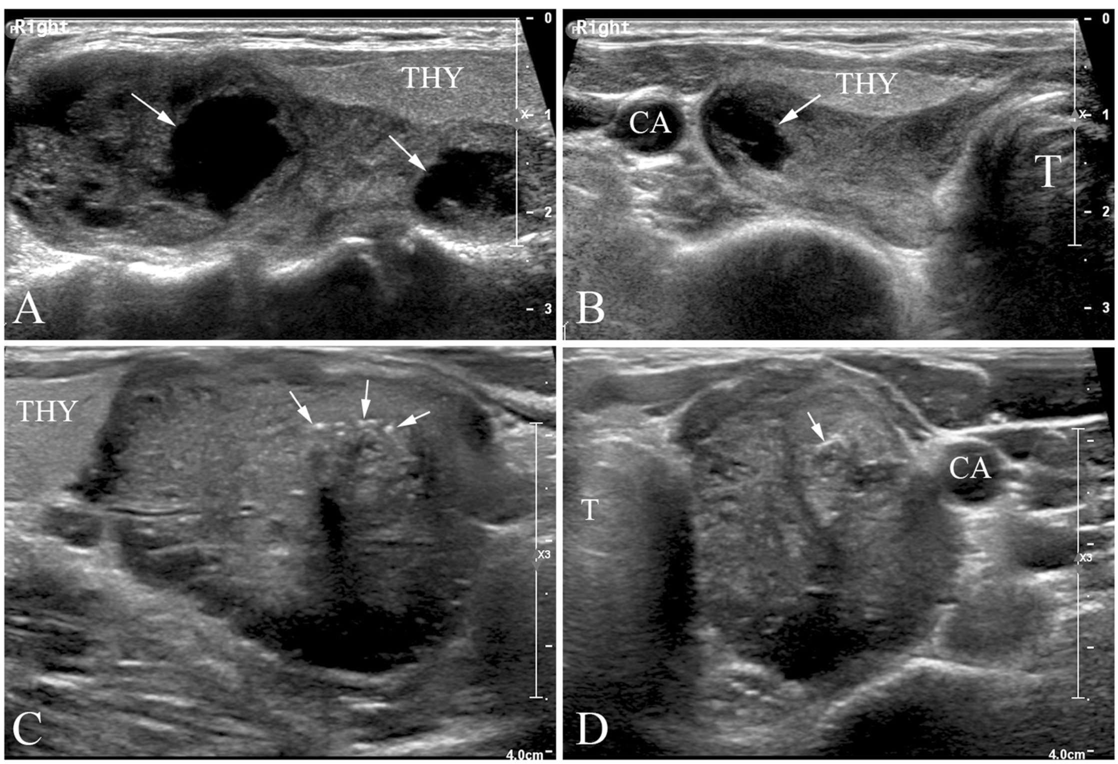

Fig. 2 **a**, **b** Ultrasonography from a 48-year-old female with parathyroid carcinoma. Longitudinal sonography (**a**) and transverse sonography (**b**) demonstrates a mixed mass with irregular shape and multifocal cystic change (arrows) against a heterogeneous echo context. **c**, **d** Ultrasonography from a 27-year-old male with parathyroid carcinoma. Longitudinal sonography (**c**) and transverse sonography (**d**) shows internal calcification (arrows) with infiltration in the margin (arrowheads). THY thyroid lobe, T trachea, CA carotid artery

CI: 1.828–20.833, $p = 0.003$), shape (OR 5.748, 95% CI: 1.149–28.759, $p = 0.033$), and infiltration (OR 30.716, 95% CI: 6.680–141.235, $p < 0.0005$). These results are summarized in Table 3. The decision curve showed that collective model with serum iPTH level involved had a better net benefit with a wider range of threshold probabilities (Fig. 3c, d).

Discussion

Parathyroid carcinoma is a rare condition that occurs in 1–5% patients with pHPT. En bloc resection of lesion with surrounding tissue was suggested for PC, but many patients experienced inadequate resection in the first operation as a

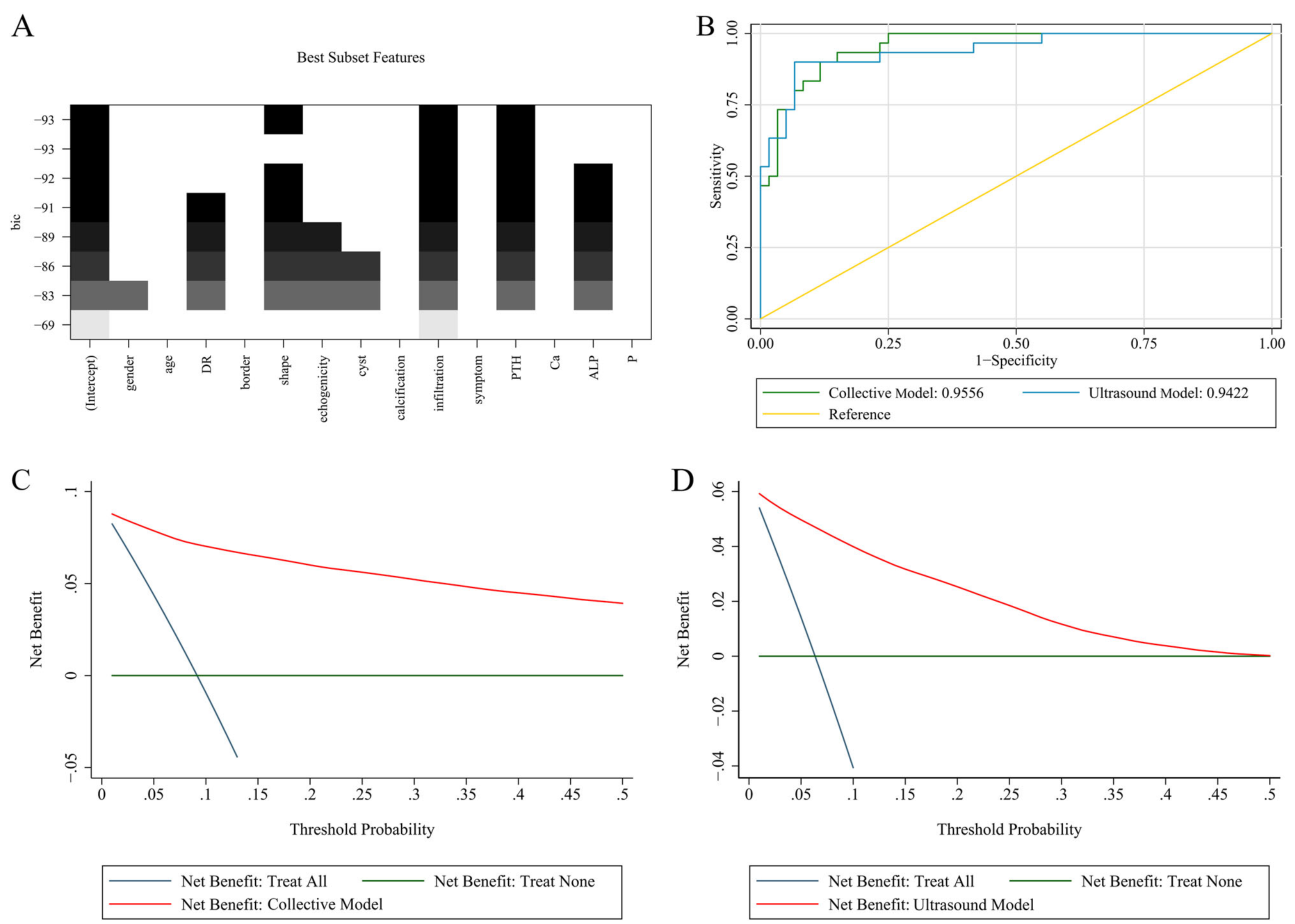

Fig. 3 The diagnostic efficacy of prediction model based on clinical and ultrasound parameters for parathyroid carcinoma. **a** Best subset features method showing different combinations of variables. It was assumed that combination of variables was better when corresponding Bayesian information criterion (BIC) value on vertical axis was lower. With three variables included (DR, infiltration, and iPTH), the lowest BIC value of −65 was obtained. **b** Receiver operating characteristics (ROC) analysis for the prediction models of parathyroid carcinoma. **c** Decision curve analysis of collective model including risk factors of iPTH, DR, and infiltration. **d** Decision curve analysis of ultrasound model including only sonographic risk factors of DR, infiltration, and shape. The horizontal green line represents the assumption that no patients will undergo radical surgery, and the oblique blue line represents the assumption that all patients will undergo radical surgery. The area under the red curve represents efficiency of prediction

matter of fact. Since arousing suspicion for malignancy prior to surgery adds confidence to the intraoperative decision making, it was important to explore the risk factors of PC preoperatively. In this study, we analyzed the US features and clinical information of PC patients enrolled from 2000 to 2018. Moreover, symptoms classification and DR, a newly defined US feature, were proposed as reference for patient diagnosis. Our research concentrated on the sporadic PC rather than hereditary forms of PC considering the extreme rarity of familial PC in Chinese population and the multiple parathyroid glands involved predilection in familial syndromes.

In line with previous findings, there were no significant differences between the two groups in terms of age and ultrasonographic location [7–9]. Disproportionate clustering by gender was, however, detected between the two groups. The fact that more male patients suffer from aggressive parathyroid carcinoma is accorded with earlier reports [10]. Cochran–Armitage test revealed that PC patients displayed more severe symptoms in our study. This result was in agreement with most previous studies [11, 12].

Serum iPTH, Ca, and ALP levels were higher in patients with PC than in those with benign disease. Consistent with the prevailing knowledge, the most promising predictor of PC according to AUC value in ROC curve was serum ALP level [13, 14]. The serum calcium level (median value of 3.20 mmol/L) in the PC group was similar to that reported previously, with cutoff value being ~2.9 mmol/L [15]. According to the logistic regression, the serum iPTH is a better predictor of malignancy compared with serum Ca or ALP. Our findings are consistent with that of McCoy et al. [16]. However, Nam et al. reported that no significant differences of iPTH and Ca level were found between PTC and PTA groups, while most of studies and clinical practice

Table 3 Multivariate analysis of variables that can independently predict occurrence of parathyroid carcinoma

	Odds ratio	95% confidence interval		Wald	*p*-value
		Lower	Upper		
Collective model					
iPTH	1.185[a]	1.047	1.341	17.082	0.007
DR	0.244	0.081	0.734	7.178	0.012
Infiltration	45.037	8.633	234.968	20.407	<0.0005
Ultrasound model					
DR	6.135	1.828	20.833	8.617	0.003
Infiltration	30.716	6.680	141.235	19.358	<0.0005
Shape	5.748	1.149	28.759	4.531	0.033

DR the maximum diameter of parathyroid lesion/the minimum diameter of parathyroid lesion (measured on sonogram)

[a]The risk is 1.185-fold higher for each 100 pg/mL increase in serum PTH

have identified higher iPTH and Ca level as risk factors of parathyroid carcinoma. This disparity may attribute to the sampling bias, different laboratory assessment systems, and ethnic diversity [8]. As in various cohorts, the sample sizes were universally small owing to the scanty cases of PC. Meanwhile, patients selected in different hospitals and time periods were presumably of varied races and experienced different generations of US equipment and biochemical assays.

Ultrasonography help differentiation between benign and malignant lesions mainly based on the gray-scale features. In this study, a series of indices including the size, shape, echogenicity, calcification, cystic change, and infiltration in addition to DR, a ratio of lesion's diameters in different dimensions, were assessed. Given parathyroid carcinoma's predilection for larger size in previous reports, a tumor size of 1.5 cm was set as the threshold in the comparison between PC and PA by Sidhu et al. [17]. So we enrolled only the cases with tumors' diameter > 1.5 cm in the present research. The median tumor size was 3.20 cm in our cohort of patients with PC, which is statistically larger than 2.61 cm in adenoma or hyperplasia. This result is consistent with a previous report comprising of 286 cases of PC, in which the size of tumors was ~3.3 cm [7]. Although most of typical adenomas are small, some of them rival carcinoma in size and gene may contribute to the variation, let alone atypical adenomas [18, 19]. To further reflect the different growth patterns between PC and PA, the D/W (depth/ width of parathyroid lesion on the transverse plane of ultrasonography) ratio was proposed by Hara et al. D/W ratio is intriguing but not always efficient probably because PC could grow toward other planes, not only on the transverse plane [8, 20]. So we calculated DR to indicate the solid growth pattern of PC [21]. Our hypothesis is that the lesion's minimum diameter on short-axis should be relatively larger and closer to maximum diameter in PC than PA. That means DR would be smaller in PC than benign lesions, and it was testified by the multivariate analysis: DR was found to be an important predictor for PC.

Infiltration on sonogram is a high-risk factor of parathyroid carcinoma with a sensitivity of 76.7% and specificity of 91.7%, respectively. Corresponding to the histopathological evidence of tissue infiltration in the diagnosis of PC, several studies have reported this phenomenon [8, 9, 17, 22]. Although infiltration was viewed as difficult to detect using US in an early research by Edmonson et al., we propose that high-resolution ultrasound settings nowadays may help to identify the presence of infiltration with more confidence. Recent studies also support our findings [8, 9, 17]. Irregular shape was predominantly observed in PC group, but it also appeared in 23 cases (38.3%) of benign group. Thus, in predicting malignancy, this feature should be considered with other sonographic risk factors such as heterogeneous echogenicity, infiltration and calcification.

Calcification was more frequently observed in PC group based on the univariate test. Despite its failure in subsequent multivariate analysis, this feature boasted a high specificity of 91.7%, which is valuable to us especially in the context of extremely low incidence of PC. This trait of PC was also emphasized in several previous studies [8, 17]. Cystic change represents hemorrhage, necrosis, and cystic degeneration, which was once reported to harbor a slightly higher risk of malignancy [21, 23]. Although some previous studies proposed the diagnostic significance of the feature, no difference concerning the cystic change between benign and malignant groups was found in the present study [9, 13, 17, 22]. Chandramohan et al. pointed out that the cystic change of parathyroid was significantly related to size and measured parathyroid hormone [23]. And our study enrolled control cases with size >1.5 cm, so cystic change may be a trait of large parathyroid lesions rather than a specific feature for malignant ones.

Recently, some researchers have recognized the difference in the elasticity of parathyroid adenoma and carcinoma [24]. This may be a result of decreased adipose tissue in parathyroid lesions [25]. As there is some overlap in sonographic appearance between PC and parathyroid benign nodules, typically atypical adenoma, shear wave elastography may provide new insight into the problem [26]. However, its precise competency is yet to be proved and we believe it is worth exploring.

Several limitations should be mentioned for this study. Firstly, the generation of the US machines used for PC group vary because of the wide time span of the present study, which also made it impossible to evaluate the color doppler characteristics of PC. Secondly, the studies performed in the early period did not provide any video or cineloop recording for review. Thirdly, because this was a retrospective study with a small cohort size, it may have some bias and sampling variation. Also, other possibly associated parameters like urinary calcium and phosphate excretion, bone resorption markers, skeletal radiological findings, and DXA-based assessment of bone mass were not available for all patients in the retrospective research, which constrained the spectrum of evaluation. In fact, we are in progress to establish a prospective database of PC and the new data may shed light on the problems mentioned above. Lastly, population bias should be considered when interpreting the results since all patients in this study are Asians.

Conclusion

In conclusion, high serum iPTH level and ultrasonographic features (DR and infiltration) are independent markers of PC. Large lesions with irregular shape, calcification, and heterogeneous echogenicity on US imaging should heighten our vigilance as well. A model based on ultrasonic features in combination with serum iPTH level may be employed as a predictive tool for PC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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