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ORIGINAL ARTICLE

Ultrasound-based scores as predictors for nodular hyperplasia in patients with secondary hyperparathyroidism: a prospective validation study

Jill Gwiasda[1] · Alexander Kaltenborn[1,2] · Jörg A. Müller[3] · Michaela Serttas[4] · Georg W. F. Scheumann[4] · Harald Schrem[1,4] · Mark D. Jäger[4]

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Abstract
Purpose Former studies evaluated echostructural and vascular patterns in ultrasound of the parathyroid gland to identify nodular hyperplasia in patients with secondary hyperparathyroidism due to chronic kidney disease. This prospective study aims to externally validate suggested ultrasound classifications.
Methods Parathyroid glands of 27 patients with secondary hyperparathyroidism undergoing parathyroidectomy were prospectively analyzed. Ultrasound including Doppler imaging was performed 1 day prior to surgery. Ultrasound data were available for 70 parathyroid glands. Echostructural and vascular scores according to previous studies were applied calculating the area under the receiver operating characteristic curve (AUROC). Overall correctness, sensitivity, and specificity of the investigated scores were assessed with the Youden index method.
Results The Doppler score introduced by Vulpio and colleagues based on characteristic blood flow patterns in parathyroid glands showed an AUROC of 0.749 for the prediction of nodular hyperplasia with an overall correctness of 72.8%. Other ultrasound classifications based on blood flow patterns, as well as echostructure of the parathyroid gland displayed AUROCs of <0.700, thus, lacking sufficient capability as a prognostic model. Overall correctness of prediction varied from 53.8 to 55.9%.
Conclusions The Vulpio Doppler score for the prediction of nodular hyperplasia in patients with secondary hyperparathyroidism was externally validated for the first time. Other ultrasound scores fail as prognostic models in this study population. Doppler sonography of the parathyroid gland has prognostic capability to identify nodular hyperplasia as surrogate marker for patients with secondary hyperparathyroidism indicating the need for ablative or surgical treatment when failing conservative therapy.

Keywords Secondary hyperparathyroidism · Parathyroid gland · Nodular hyperplasia · Ultrasound · Prognostic score

Jill Gwiasda and Alexander Kaltenborn contributed equally.

✉ Jill Gwiasda
gwiasda.jill@mh-hannover.de

[1] Core Facility Quality Management and Health Technology Assessment in Transplantation, Integrated Research and Treatment Center-Transplantation (IFB-Tx), Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany

[2] Department of Trauma and Orthopaedic Surgery, Federal Armed Forces Hospital Westerstede, Westerstede, Germany

[3] Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany

[4] Department of General, Visceral and Transplant Surgery, Hannover Medical School, Hannover, Germany

Background

Nodular hyperplasia of the parathyroid gland has been identified as the key issue for the failure of medical treatment in patients with secondary hyperparathyroidism (sHPT) due to chronic renal failure [1]. A broad spectrum of therapy options is available. However, vitamin D analoga and phosphate binders do not stop the course of the disease, whereas calcimimetics are thought to reduce the occurrence of severe sHPT [2]. Nevertheless, the debate on the usefulness of medical therapy with calcimimetics opposed to a timely parathyroidectomy regarding long-term outcome is ongoing. So far, there is no randomized clinical trial available to compare the

outcome of those therapy options for patients with end-stage renal insufficiency.

In addition to that, two prospective randomized studies were recently conducted, which analyzed patients with long-term hyperparathyroidism after kidney transplantation to compare the outcome of medical therapy with calcimimetics opposed to a parathyroidectomy. The group around Cruzado and colleagues found surgical therapy to be more effective in controlling hypercalcemia than medical therapy with calcimimentics [3]. On the other hand, a research group from the University of Cairo did not describe significantly differing results between the two therapy options, especially when looking at the iPTH level [4]. Another retrospective trial from Groningen analyzed the effects of calcimimetics on the timing of parathyroidectomy and found patients with sHPT to undergo surgery about 2 years later than a reference group without medical treatment with calcimimetics [5]. In spite of the use of calcimimetics, an elevated iPTH level was observed in those patients prior to parathyroidectomy [5].

In conclusion, the usefulness or even superiority of medical therapy with calcimimetics opposed to a parathyroidectomy on long-term outcome on patients with sHPT remains unclear.

However, in patients suffering from severe sHPT with the pathological tissue change to nodular hyperplasia of the parathyroid gland, calcimimetics, which are known to effectively reduce the secretion of parathormone and the volume of parathyroid glands, are thought to fail to control the disease [6–8]. Hence, the presence of nodular hyperplasia could be interpreted as surrogate marker indicating a typical obstacle for successful medical treatment in sHPT patients. Therefore, non-invasive identification of nodular hyperplasia of parathyroid glands should lead to a critical consideration of treatment options including escalation of medical treatment, focused ablation, and/or targeted surgical resection of severely diseased parathyroid glands [9].

Several studies have identified ultrasound (US) to be a valuable tool to identify parathyroid glands with nodular as opposed to diffuse hyperplasia [10–12]. Multiple parameters such as the vascular or the echostructural pattern, as well as the maximum longitudinal diameter and weight of the parathyroid glands have been assumed to correlate with nodular hyperplasia [11, 13, 14]. Some of these parameters have been used in a number of US-based scores, which were introduced as a stratified tool to simplify diagnosis of nodular hyperplasia [10–12]. The reported results of sonography in parathyroid gland hyperplasia can be summarized as promising [15].

The current study focuses on three published US-based scores. Two of these scores are based on the Doppler signal to identify the blood flow in the center and periphery of parathyroid glands as introduced by Onoda and colleagues in 2003 and Vulpio et al. in 2008 [10, 11]. Another US score, also introduced by Vulpio et al. in 2008, categorizes parathyroid glands according to their echostructural pattern and thus does not rely on Doppler imaging [11].

The current study is a timely contribution to the recent debate on the assessment of parathyroid glands by sonography and aims to validate said US-based scores.

Patients and methods

Study population

Included in this prospective study population were 27 patients (age ≥18 years) undergoing parathyroidectomy between 2008 and 2010 at Hanover Medical School, Germany. Indications for parathyroidectomy ranged from preventive resection and patients with cinacalcet treatment to patients suffering from severe sHPT with lack of response to medical therapy. None of the patients in the current study cohort underwent kidney transplantation.

Ultrasound examination

During surgery, a total of 108 parathyroid glands were resected. US data was available for 70 parathyroid glands and Doppler imaging data for 51 parathyroid glands.

Standardized US including Doppler imaging was performed by a single physician with more than 20 years of experience in US of thyroid and parathyroid glands. It was performed 1 day prior to parathyroidectomy using Sonoline Sienna equipment (Siemens, Erlangen, Germany) with a linear array (7.5 MHz, 7 cm in length). Standardized photo documentation included topographical anatomy of the thyroid, parathyroid glands, and surrounding structures. The detection of parathyroid glands by US was matched with the topographical findings during parathyroidectomy and confirmed by histology.

Blood flow signals were classified in ordinal scale at periphery (P-Signal 0–2) and in the center of parathyroid glands (C-Signal 0–2) according to the original publications which introduced the investigated US scores [10, 11]. Both studies combined P- and C-Signals to define vascular patterns for each gland. Both scores were divided and categorized in ordinal scale as previously published (labeled as “Doppler score Onoda” 0 to 3 and “Doppler score Vulpio” 1 to 3) (see Table 1).

The echostructural pattern (EP) of parathyroid glands was classified in an ordinal scale according to the former study published by Vulpio et al. (EP 1 = hypoechoic homogeneous, 2 = slightly heterogeneous, 3 = highly heterogeneous, 4 = nodular) [11]. Accordingly, stages 1 and 2 were associated with diffuse hyperplasia, whereas stages 3 and 4 mainly occurred in parathyroid glands with nodular hyperplasia (labeled as “Echostructural pattern Vulpio”) (see Table 1).

Table 1 Shown are the three analyzed ultrasound scores and their distribution into nodular versus non-nodular

		Nodular (*n*)	Non-nodular (*n*)
Doppler score Onoda	P0, C0	7	8
	P1/2, C0	2	12
	P0/1/2, C1	11	6
	P0/1/2, C2	4	1
Doppler score Vulpio	P1/2, C1	3	12
	(P1/2+ C1), C2	10	6
	P1/2+ C2	4	1
Echostructural pattern Vulpio	Hypoechoic homogeneous	7	6
	Slightly heterogeneous	15	20
	Highly heterogeneous	8	10
	Nodular	4	0

P peripher signal, *C* central signal

Clinical examination

Laboratory values were determined according to study protocol 1 day prior to surgery. All parathyroidectomies were performed by two experienced endocrine surgeons. A routine cervical thymectomy was performed in all cases. All located parathyroid glands were documented exactly in correspondence to surrounding structures.

Histological classification

All the resected parathyroid glands were histologically examined at least at five levels. The pattern of hyperplasia was classified as proposed by Tominga et al. [8]. Each parathyroid gland was categorized as nodular or non-nodular hyperplasia based on this classification.

Statistical analysis

Receiver operating characteristic (ROC) curve analyses were deployed to calculate the sensitivity, specificity, and overall model correctness of the investigated scores to assess their prognostic and diagnostic capabilities to detect nodular hyperplasia. Areas under the ROC-curves (AUROCs) larger than 0.700 indicate by definition useful prognostic or diagnostic models [16]. Cut-off values of the potential prognostic/diagnostic models were determined with the best Youden index (Youden index = sensitivity + specificity – 1) [17]. The Hosmer-Lemeshow Chi2-statistic goodness-of-fit test was applied to assess model calibration of binary logistic regression models. These statistics suggest good fit when the associated *p* values are greater than 0.05 [18]. Binary logistic regression was performed as additional test to determine the influence of the investigated scores on the study endpoint. A power level of 0.70 was defined as significant to calculate required sample size. For all statistical tests, a p value <0.05 was defined as significant. The SPSS statistics software version 22.0 (IBM, Somers, NY, USA) was used to perform statistical analysis.

Results

Clinical characteristics of the patients and examined parathyroid glands are summarized in Tables 2 and 3. Sixty-five percent of parathyroid glands (70 of 108) were detected by US. The distribution of nodular versus non-nodular hyperplasia detected by US was almost equal (n = 34 (48.6%) versus n = 36 (51.4%), see Table 3). Of the resected 108 parathyroid glands, nodular hyperplasia was histologically confirmed in 43.5% (n = 47). The measured volume of parathyroid glands with nodular hyperplasia was significantly larger than the volume of glands with diffuse hyperplasia (p = 0.003, see Table 3). Analysis of 70 US-detected parathyroid glands was shown to have a statistical power of 0.74.

The Doppler score according to Vulpio et al. reached AUROCs >0.700 for the prediction of nodular hyperplasia of parathyroid glands [11]. The Doppler score according to Onoda et al., as well as the US classification based on echostructural pattern, each displayed AUROCs of <0.700 (see Table 4) [10, 11].

Doppler score according to Onoda et al.

With an AUROC of 0.640, this Doppler-US-based score could not demonstrate relevant prognostic capabilities in ROC-curve analysis (Fig. 1). Furthermore, a significant Hosmer-Lemeshow test revealed a lack of fit of this score's regression model with the investigated dataset (p = 0.026). Overall correctness of prediction was assessed at 55.9%, whereas sensitivity was 11.8% and specificity was 100%.

The Onoda-score showed a trend towards an increased odds ratio as factor for the identification of nodular

Table 2 Shown are the clinical characteristics of the patients in this study. The study population is subdivided according to the severity of sHPT, elucidating the indications for parathyroidectomy

Variable	Preventive PT $n = 8$	sHPT, iPTH ≤ 800 pg/dl, no cinacalcet $n = 45$	sHPT, iPTH ≤ 800 pg/dl, with cinacalcet $n = 35$	sHPT, iPTH ≥ 800 pg/dl, with cinacalcet $n = 20$	Mean (SD) total PG $n = 108$
Age in years	69 (9)	47 (15)	57 (9)	50 (16)	52 (14)
Body mass index (kg/m^2)	29.0 (0.9)	29.7 (7.5)	26.6 (6.3)	24.9 (3.1)	27.7 (6.4)
Duration of dialysis in years	0	5.2 (4.2)	5.5 (2.4)	5.6 (3.6)	4.9 (3.7)
GFR (ml/min)	20.0 (0.9)	7.6 (2.4)	8.9 (1.6)	8.6 (3.0)	9.1 (3.8)
Calcium (mmol/l)	2.5 (0.1)	2.6 (0.1)	2.3 (0.1)	2.4 (0.1)	9.8 (0.6)
iPTH (pg/dl)	483.5 (28.3)	531.6 (97.2)	458.1 (151.2)	1198.5 (291.8)	627.7 (319.5)
Phosphorus (mmol/l)	1.4 (0.1)	1.9 (0.6)	1.5 (0.4)	2.1 (0.5)	2.4 (0.2)
1,25-$(OH)_2$-vitamin D (pmol/l)	43.9 (13.4)	13.7 (9.7)	18.2 (12.3)	9.9 (7.1)	16.8 (13.3)

PT parathyroidectomy, *sHPT* secondary hyperparathyroidism, *iPTH* intact parathyroid hormone, *SD* standard deviation, *PG* parathyroid gland, *GFR* glomerular filtration rate

hyperplasia with sonography without reaching statistical significance ($p = 0.076$; OR 1.716; 95%-CI 0.946–3.133).

Doppler score according to Vulpio et al.

The AUROC for the vascular pattern score according to Vulpio et al. was 0.749 (Fig. 2) with a good model fit ($p = 0.532$). Univariate binary logistic regression revealed that the Vulpio Doppler score was identified as a statistically significant factor for intra-operatively confirmed nodular hyperplasia of the parathyroid glands ($p = 0.011$; OR 4.825; 95%-CI 1.424–16.349). The overall correctness was assessed at 72.8%, whereas sensitivity and specificity were 63.2 and 82.4%, respectively.

Echostructural pattern classification according to Vulpio et al.

ROC-curve analysis of the echostructural pattern showed an AUROC of 0.533 indicating a lack of prognostic capability for the prediction of nodular hyperplasia in parathyroid glands in the investigated population (Fig. 3). The Hosmer-Lemeshow test excluded significant lack of model fit ($p = 0.109$). The overall correctness of prediction was assessed at 53.8% with specificity of 72.2% and a sensitivity of 23.5%. Univariate binary logistic regression revealed a trend that the echostructural pattern might predict nodular hyperplasia although it did not reach statistical significance ($p = 0.423$; OR 1.275, 95%-CI 0.704–2.310).

Discussion

Sonography is a promising prognostic tool for the prediction of nodular hyperplasia of parathyroid glands in patients with sHPT. The previously introduced Doppler score according to Vulpio and colleagues could be externally validated for the first time, whereas the echostructural score according to Vulpio et al., as well as the Doppler score according to the Onoda group, did not show prognostic capabilities in the current study population [10, 11].

The need for the identification of nodular hyperplasia of the parathyroid gland in patients with non-response to conservative treatment is immense [6, 19]. Furthermore, large gland sizes of >10 mm are associated with nodular hyperplasia, which can be interpreted as a surrogate marker for the failure of medical treatment in patients with sHPT [6]. With the availability of calcimimetics, there seems to be a widening gap between patients with good response to medical therapy and those without, who are labeled as non-responders. Although

Table 3 Shown are the ultrasound characteristics of parathyroid glands of this study

Variable	*p* value	Nodular	Non-nodular	Total	
				n	Mean (SD)
PG resected	n.a.	47 (43.5%)	61 (56.5%)	108	
Vol. of PG PT (mm^3) as mean (SD)	<0.001	1311 (1170)	474		838 (939)
PG US detected	n.a.	34 (48.6%)	36 (51.4%)	70	
Vol. of PG US (mm^3) as mean (SD)	0.003	1061(1060)	320 (305)		680 (851)

PG parathyroid gland, *Vol.* volume, *PT* parathyroidectomy, *US* ultrasound, *SD* standard deviation

Table 4 Shown are the results of receiver operating characteristic curve analyses of previously suggested ultrasound scores

Variables	AUROC	95%-CI	Sens.	Spec.	OC	UBLR	HL
Doppler score Onoda (0–3)	0. 640	0.481–0.800	11.8	100	55.9	$p = 0.076$ OR 1.716 95%-CI 0.946–3.133	$p = 0.026$
Doppler score Vulpio (1–3)	0. 749	0.586–0.912	63.2	82.4	72.8	$p = 0.011$ OR 4.825 95%-CI 1.424–16.349	$p = 0.532$
Echostructural pattern Vulpio (1–4)	0. 533	0.396–0.671	23.5	72.2	53.8	$p = 0.423$ OR 1.275 95%-CI 0.704–2.310	$p = 0.109$

AUROC area under the receiver operating characteristic curve, *95%-CI* 95%-confidence interval, *Sens.* sensitivity, *Spec.* specificity, *OC* overall correctness, *UBLR* univariate binary logistic regression, *HL* Hosmer-Lemeshow

p values of <0.05 were considered statistically significant

the long-term results for medical therapy with calcimimetics opposed to parathyroidectomy remain uncertain due to the lack of randomized clinical trials, last therapeutic resort in non-responders is still parathyroidectomy. Therefore, reliable detection of nodular hyperplasia in parathyroid glands is a relevant clinical issue to discriminate non-responders that might profit from surgical intervention or ablation.

Sonography is an inexpensive, non-invasive method to evaluate parathyroid glands and has been shown to be highly sensitive in experienced hands [9]. However, recent studies reported the major limitation of US to be highly operator dependent with detection rates of parathyroid gland abnormalities varying from 70 up to 96% [9]. Therefore, a structured US examination with the aid of pre-defined US-based scores likely facilitates more reliable and reproducible results of parathyroid gland sonography. This aspect further strengthens the promising results of the current study, which identified the Vulpio Doppler score as a reliable tool. Moreover, the Onoda Doppler, as well as the Vulpio echostructural pattern score were both shown to have potential usefulness, since a trend towards increased odds ratios for the identification of nodular hyperplasia was observed. Nevertheless, these analyses did not reach statistical significance.

The major strength of this study is the variety of patients that were observed with a broad spectrum of sHPT severity reaching from preventive parathyroidectomy to severe sHPT with lack of response to medical therapy. Also, the current study cohort displayed an almost equal ratio of patients with nodular versus non-nodular hyperplasia ($n = 34$ (48.6%) versus $n = 36$ (51.4%), see Table 3). Onoda and colleagues examined a study cohort, in which 70% (44 of 63 glands) were nodular hyperplastic, which might result in more likely US findings, since small, healthy parathyroid glands are far more difficult to detect. On the other hand, if these parathyroid glands are detected by a well-trained US examiner, they can quite easily be identified as non-nodular hyperplastic.

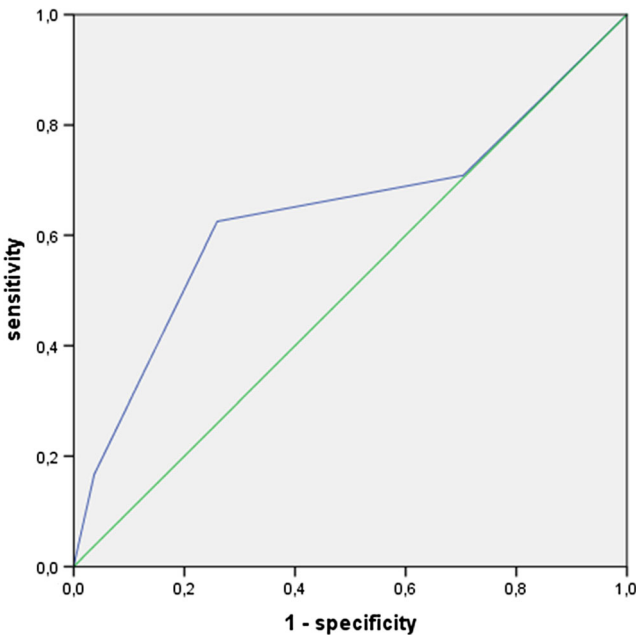

Fig. 1 Shown is the receiver operating characteristic curve of the Doppler score according to Onoda et al. (AUROC 0.640)

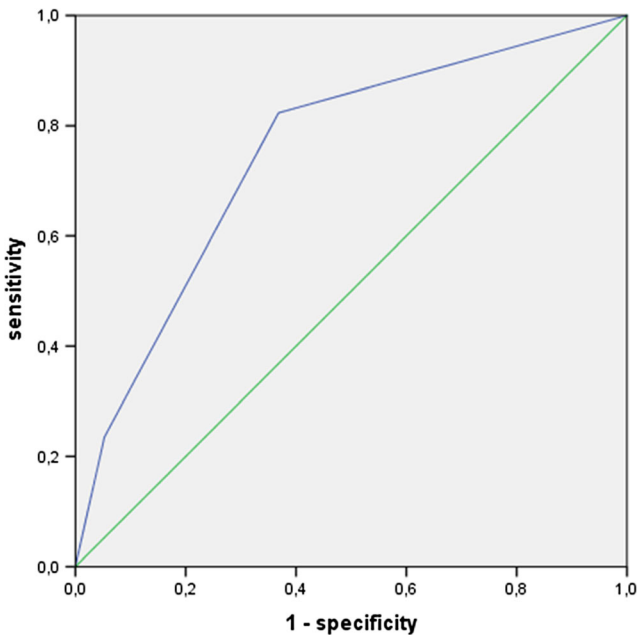

Fig. 2 Shown is the receiver operating characteristic curve of the Doppler score according to Vulpio et al. (AUROC 0.749)

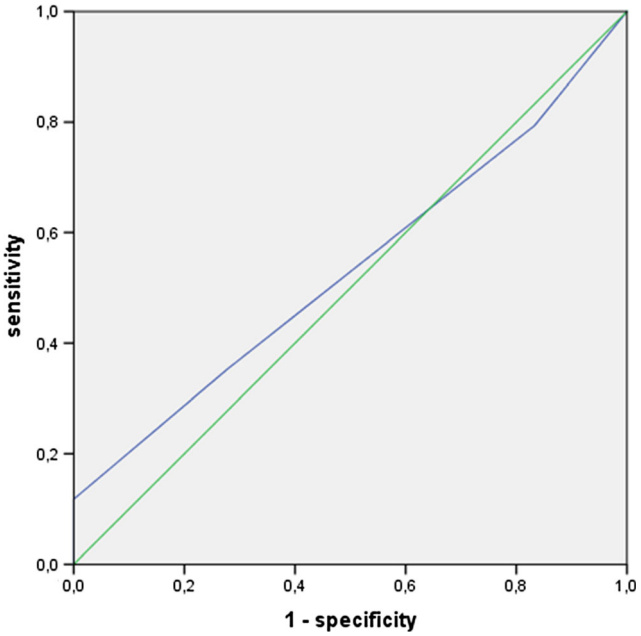

Fig. 3 Shown is the receiver operating characteristic curve of the echostructural score according to Vulpio et al. (AUROC 0.533)

Keeping this in mind, it seems to be even more striking that the score Vulpio et al. developed has superior prognostic capabilities in an external cohort completely independent from the dataset which has been used for score development. Furthermore, Vulpio and colleagues were only able to histologically confirm a part of their US study cohort ($n = 45$) [11]. In the current study on the other hand, all patients underwent subsequent parathyroidectomy, so glands and their characteristics were histologically classified in all cases. US were performed by an experienced examiner. This aspect granted a high quality of US examinations for this study which might not be easily replicated in other studies. Despite the well-documented different vascular patterns of parathyroid glands, it remains to some extend subjective to classify slight versus high blood flow patterns. However, especially, both Doppler scores can easily be obtained with basic US equipment and a systematic examination.

When looking at the echostructure of the parathyroid gland, it has to be acknowledged that superior US equipment may show different, more detailed findings which may limit universal applicability.

Both Doppler scores according to Onoda and Vulpio are based on the measured blood flow pattern in the parathyroid glands, indicating that those glands with increased blood flow are nodular hyperplastic [10, 11]. The Vulpio score is slightly more complex regarding the possible combinations of signals measured in the center and periphery (see Table 1). It appears noteworthy that only the Vulpio score shows sufficient prognostic and diagnostic capabilities highlighting the relevance of blood flow pattern classification. The key feature of Doppler-scoring is the detection of a relevant Doppler signal centrally in the parathyroid gland, which is easily and reliably repeatable using standard US-Doppler setting.

A limiting factor is the study's single-center design. Due to the fact, that parathyroid glands without blood flow were excluded from calculation in the Vulpio score, there were only 36 parathyroid glands in the validation cohort. A prospective study with a larger cohort would be useful. Moreover, it needs to be kept in mind that the calculated power is only representative for the cohort of all sonographically confirmed parathyroid glands. Therefore, the sample sizes of the sub-cohorts for score calculations might be slightly underpowered and the results of this study should be confirmed in a larger population. Despite of the prospective study design and prospective ethics approval, the study was retrospectively registered at www.researchregristry.com with the unique identifying number (UIN) research registry1894 according to the Declaration of Helsinki.

On the basis of the recent literature, future studies should further consider other clinical parameters which might well be correlated with nodular hyperplasia, such as the iPTH level, or the maximal longitudinal diameter of the parathyroid glands, which are not taken into account in the investigated scores [1, 6, 7].

It can be summarized that developing a new prognostic score with additional clinical parameters potentially leads to an improved prognostic or diagnostic model to foster individual parathyroid gland therapy. The design of such a study would follow the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidelines. The TRIPOD guidelines had not been published when the investigated US scores were developed [20].

Conclusion

The Vulpio Doppler score for the prediction of nodular hyperplasia in patients with secondary hyperparathyroidism was externally validated for the first time. Other ultrasound scores fail as prognostic models in this study population. Doppler sonography of the parathyroid gland has prognostic capability to identify nodular hyperplasia as surrogate marker for patients with secondary hyperparathyroidism indicating the need for ablative or surgical treatment when failing conservative therapy.

Most recently, Vulpio et al. also suggested to merely apply US as a part of a new predictive model which also includes clinical parameters such as the iPTH level, in order to define a robust diagnostic prognostic model to guide the indication for medical, ablative, or surgical therapy [11]. The findings of this study underline this statement, indicating that the identification of nodular hyperplasia of parathyroid glands might function as surrogate marker for the failure of medical treatment in patients with sHPT.

Authors' contributions Study conception and design: J. G., A. K., H. S., M. D. J. Acquisition of data: J. G., A. K., J. A. M., M. S., G. W. F. S., H. S., M. D. J. Analysis and interpretation of data: J. G., A. K., J. A. M., M. S., G. W. F. S., H. S., M. D. J. Drafting of manuscript: J. G., A. K., H. S., M. D. J. Critical revision of manuscript: J. G., A. K., J. A. M., M. S., G. W. F. S., H. S., M. D. J.

Compliance with ethical standards

Ethics approval and consent to participate The study was approved by the institutional ethics committee on August 13th 2007 and was conducted in accordance with the guidelines published in the Declaration of Helsinki and retrospectively registered www.researchregistry.com with the unique identifying number (UIN) research registry1894.

Competing interests The authors declare that they have no competing interests.

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