Original Article

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Laboratory Parameters Predict Complications in Primary Hyperparathyroidism: A Multicenter Cross-sectional Study

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Abstract

Aim: There is no study predicts the development of complications with laboratory parameters in patients with primary hyperparathyroidism (PHPT). We aimed to determine the laboratory parameters that predict the development of osteoporosis or nephrolithiasis in patients with PHPT and identify high-risk patients.

Methods: This multicenter retrospective cross-sectional study was conducted between January 2018 and January 2020. The study group consisted of 389 patients who were diagnosed with PHPT (68 patients without surgical indications and 321 patients with PHPT who underwent surgery), and 451 individuals without any additional disease as a control group. Patients' data was obtained from the hospital automation system. All patients were divided into three groups (control, unoperated and operated), and laboratory parameters were compared.

Results: The Wisconsin index (WIN), which is used to detect hyperfunctional glands in addition to parathyroid adenoma in PHPT, and the Parathyroid functional index (PFIndex), which is used to differentiate HPT secondary to vitamin D deficiency, can identify patients at high risk of nephrolithiasis or osteoporosis in patients with PHPT. In patients who have been operated on due to PHPT-related complications, the WIN value of 283.29 showed 95% sensitivity and 72% specificity in predicting osteoporosis, while the PFIndex of 36.43 had 86% sensitivity and 68% specificity for predicting nephrolithiasis.

Conclusion: The WIN and PFIndex can be used to refer patients with PHPT for surgery before the onset of osteoporosis or nephrolithiasis. Although no risk factor could be found for nephrolithiasis, WIN was found as an independent risk factor for osteoporosis.

Keywords: Hyperparathyroidism, nephrolithiasis, osteoporosis, parathyroid functional index, Wisconsin index

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder that causes abnormalities in serum calcium (Ca) and phosphorous (P) levels (1). An increase is observed in serum parathormone (PTH) and Ca levels, and hypophosphatemia may occur at a rate of 10-20% (2,3). Because it is converted to 1.25-(OH)2-Vit D with an increase in renal alpha-hydroxylase activity, 25-OH-Vit D levels can be lower than normal (4). PTH activity is suppressed with 25-OH-Vit D replacement without an increase in serum Ca levels (5,6).

Changes caused by serum PTH levels in Ca, P, and 25-OH-Vit D levels have been used in the diagnosis of PHPT in several studies. Madeo et al. (1) reported that the ratio of serum Ca level to P (Ca/P) level was revealed to be an important marker in the diagnosis of PHPT. Guo et al. (7) developed the parathyroid function index (PFIndex), which is obtained by multiplying the Ca level by

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the PTH level and then dividing the product by the serum P level (Ca×PTH/P), to differentiate secondary vitamin D deficiency HPT (VD-SHPT) from normocalcemic PHPT (NC-PHPT) (7,8). This term was used for the first time in their study in 2020. Mazeh et al. (9) developed the Wisconsin index (WIN) by multiplying the PTH level by the Ca level. This index has been used as an intraoperative index to predict further gland hyperfunctioning (9). However, none of these parameters has been associated with surgical indications.

In addition to all these studies, no study predicts the development of complications with laboratory parameters in patients with PHTH. Thus, this study used the close relationships between Ca, P, PTH, and 25-OH-Vit D levels as parameters that could predict the presence of osteoporosis and nephrolithiasis. Therefore, we investigated the ratio of Ca, P, PTH, Ca/P and serum PTH levels at the time of presentation to the 25-OH-Vit D level (PTH/VitD), the ratio of serum PTH and Ca levels to the serum 25-OH-VitD level (PTH×Ca/Vit D), and the relationship between WIN and PFIndex in patients with and without surgical indications for osteoporosis and nephrolithiasis to identify the parameters that could refer these patients for surgery before the onset of osteoporosis and nephrolithiasis.

Methods

Ethical Approval

This study was approved by the local ethics committee of Yozgat Bozok University, Faculty of Medicine (Ethics Committee no: 2017-KAEK-189_2020.10.14_01).

Study Design and Sample Size

This multi-centre cross-sectional study was conducted between January 2018 and January 2020. Data of patients were obtained from Yozgat City Hospital, Hitit University, Erol Olcok Training and Research Hospital, and Amasya Serefeddin Sabuncuoglu Training and Research Hospital. The study group consisted of 389 patients who were diagnosed with PHPT, and the control group consisted of the first 451 individuals who were admitted to the outpatient clinic with no comorbid diseases. Patients' age, sex, comorbid diseases, and drugs used were obtained from the hospital database and then recorded. The first recorded laboratory values were included in the analysis.

The diagnosis was NC-PHPT if the serum Ca level was within the laboratory reference range and the PTH level was above the reference range, PHPT if the serum Ca and PHT levels were above the reference range, and normohormonal PHPT if the serum Ca level was high, but the PTH level was within the normal range. The exclusion criteria were as follows: pregnant women: patients aged <18 years; patients with 25-OH-Vit D deficiency; renal failure (GFR<90 mL/min); chronic liver failure; congestive heart failure; malabsorption syndrome and malignancy history; patients with hypercalciuria; patients who used drugs such as thiazide, lithium, bisphosphonate, and denosumab; patients with familial hypocalciuric hypercalcaemia; and patients whose serum Ca level was more than 1 mg/dL above the upper normal limit of the laboratory reference range. The criteria stated in the Guideline for the Management of Asymptomatic PHPT in the Fourth International Workshop were accepted as indications for surgery in patients included in the study. These criteria are as follows: age <50 years, serum Ca level >1 mg/dL according to the upper bound of the laboratory reference range, 24-h urinary Ca excretion >400 mg/day, GFR <60 mL/min, dual-energy X-ray absorptiometry (DEXA), and a T-score ≤−2.5 or the presence of fracture in vertebral imaging and the presence of nephrolithiasis or nephrocalcinosis in renal imaging (10). Patients who did not meet these criteria were not operated.

Laboratory Assessment

Venous blood samples of the patients were collected after a mean of an 8 h fast. Xylidyl blue methods (Beckman Coulter AU 5800 analyser, Beckman Coulter Inc., USA) were used to measure serum creatinine (Cr, 0.6-1.17 mg/dL), Ca (8.5-10.5 mg/dL), 24-h urinary Ca (photometric), albumin (3.5-5.2 mg/dL), bromocresol green, and P (2.5-4.5 mg/dL). Serum Ca levels were corrected using the formula of [0.8 × (4.0-albumin) + serum calcium] according to serum albumin measurements. Serum intact PTH (1-84) (12-88 pg/mL) and 25-OH-D (ng/mL) levels were measured using chemiluminescent immunologic tests (Beckman Coulter DXI 800 device).

The PFIndex was calculated by dividing the product of serum PTH level (pmol/L) and the corrected Ca level (mmol/L) by the serum P level (mmol/L) (PFIndex=Ca×PTH/P) (7). WIN was calculated by multiplying the serum PTH level (pg/mL) by the corrected Ca level (mmol/L) (WIN=Ca×PTH) (8).

The indices we developed for the study were the serum PTH (pg/mL) level to 25-OH-Vit D (ng/mL) ratio (PTH25-OH-VitDR) and the ratio of multiplying the serum PTH (pg/mL) level and serum Ca (mg/dL) level, divided by the 25-OH-Vit D level (ng/mL) (PTH×Ca/25-OH-Vit D).

Imaging Methods

Renal ultrasound (US) was performed by radiologists for nephrolithiasis and nephrocalcinosis. Bone mineral density (BMD) was measured using DEXA (Hologic QDR4500 device, Hologic Inc., Waltham, MA, USA). L1-4, total hip, femoral neck, and the distal one-third of the radius were evaluated. T-score <-2.5 was considered to have osteoporosis (11).

Statistical Analysis

Data analysis was performed using the SPSS 20 (IBM Corp, Armonk, NY, USA) software. The data is presented in the form of a mean, standard deviation, and percentiles. The normality distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and that of numerical data was assessed using the non-parametric Kruskal-Wallis tests. A parametric one-way analysis of variance (ANOVA) was used for normally distributed variables, and post hoc assessment was performed using Bonferroni correction. The non-parametric Mann-Whitney U test was used for two-group comparisons of non-normally distributed numerical data, and the parametric Student's t-test was used for normally distributed numerical data. In the multivariate analysis, possible factors detected in the univariate analyses were analyzed in the logistic regression analysis to further identify independent parameters that could predict the onset of osteoporosis. The threshold value affecting osteoporosis and nephrolithiasis was determined using receiver operating characteristic (ROC) curve analysis. A p-value <0.05 was set as a significant result.

Results

The patients were divided into three groups: the control group, the PHPT group with surgical indications and the PHPT group without surgical indications. Laboratory parameters were compared among the groups in Table 1. PTH, PTH/VitD, PFIndex, PTH×Ca/Vit D, and WIN values were significantly higher in the PHPT group with surgical indications than in the PHPT group without surgical indications ($p<0.001$) (Table 1).

Laboratory parameters of those with osteoporosis or nephrolithiasis and those without surgical indications among patients with PHPT were compared separately. Compared with the group without surgical indications, significant differences were found in all parameters other than serum P level in patients with osteoporosis ($p<0.05$) (Table 2). Serum Ca, PTH, and urinary Ca levels, as well as Ca/P, PTH/VitD, PFIndex, and PTH Ca/Vit D and WIN values, were significantly higher in nephrolithiasis patients, while age and serum P levels were significantly lower (Table 2).

Indicators that could predict the development of osteoporosis and nephrolithiasis were assessed in the ROC curve analysis, and the calculated area under the curve values are shown in Table 3. The cut-off value of 283.29 for WIN had a sensitivity of 95% and a specificity of 72% for detection of osteoporosis. Moreover, the cut-off value of 36.43 for the PFIndex had a sensitivity of 86% and specificity of 68% to predict concomitant nephrolithiasis (Table 3, Figure 1). The values were considered in the multivariate logistic regression analysis for osteoporosis and nephrolithiasis. Although no risk factor could be found for nephrolithiasis, WIN was found as an independent risk factor for osteoporosis (odds ratio of 1.507, 95% confidence interval: 1.01-1.71) (Table 4, Figure 2).

Discussion

The prevalence of asymptomatic PHPT in the general population is 80%, and it may cause complications in the bones and kidneys (4). However, predicting these complications is difficult, and no laboratory parameters have been confirmed to predict the development of complications. In this study, WIN and PFIndex demonstrated high sensitivity and specificity in predicting osteoporosis and nephrolithiasis. Additionally, multivariate logistic analysis of laboratory parameters that showed potential risk in the development of osteoporosis revealed WIN as an independent risk factor. These findings can be used as important markers in decision-making when referring patients for surgery before the onset of osteoporosis and nephrolithiasis. The low and high-risk groups in terms of nephrolithiasis and osteoporosis can be determined by the obtained results. Therefore, patients in the low-risk group can be followed up only with routine blood parameters and urinary Ca excretion instead of BMD and renal US. Complications can be evaluated for patients in that high-risk group, or they can be referred for surgery.

Mazeh et al. (9) recommended using WIN as a parameter during parathyroid surgery to predict additional gland hyperfunctioning. They concluded that this parameter was more practical and useful than waiting for intraoperative PTH results in terms of the presence of an additional functional gland after minimally invasive parathyroidectomy. However, in a recent study, WIN was not found to be more successful than intraoperative PTH in patients with multi-glandular parathyroid disease (12). Guo et al. (7) used the PFIndex to successfully differentiate NC-PHPT from VD-SHPT. Guo et al. (7) used WIN in the differential diagnosis of PHPT and NC-PHPT, but it was not as successful as the PFIndex. There is no other study in the literature about PFIndex for predicting operation indications in patients with PHPT. None of these indices have been associated with the presence of complications. Previous studies have identified demographic and laboratory data as risk factors in the development of complications. However, no cut-off value that could predict the existence of complications has been proposed. Thus, the parameters identified in this study can be used to decide which patients can undergo surgery among those without complications.

The presence of osteoporosis in PHPT is associated with the resorption of Ca from the bones, as well as

the direct effects of increased PTH and fibroblast growth factor 23 (FGF-23) levels on the bones (13). Abnormalities in the cortical structure are often observed in bones. The incidence of osteoporosis can be as high as 39-62% (14). Bone fractures are present in 21% of patients at the time of diagnosis of PHPT (15). This was linked to the decrease in the trabecular bone score and was associated with the deterioration in bone microarchitecture. BMD improves in all regions, and vertebral fractures decrease with surgery in patients with PHPT and osteoporosis (4,16). In the study by Lundstam et al. (16), although no vertebral fractures developed

Table 1. Comparison of laboratory data of the control group, the PHPT group without a surgical indication, and the PHPT group that underwent surgery

	Control group n=451	PHPT n=389		
	F/M: 351/100	Unoperated n=68 F/M: 58/10	Operated n=321 F/M: 278/43	p
Age (years)	54.7±5.6	60.4±7[a,c]	55.4±12.1	<0.001[&]
Ca (mg/dL)	9.4±0.4[b,c]	10.8±0.4	11±0.4	<0.001[µ]
P (mg/dL)	3.3±0.5[b,c]	2.7±0.5	2.5±0.5	<0.001[&]
Cr (mg/dL)	0.9±0.3[b,c]	0.8±0.2	1±5	<0.001[µ]
PTH (pg/mL)	56.2 24.9[b,c]	148.3±60.7[c]	223.4±147.2	<0.001[µ]
25-OH-VitD (ng/mL)	17±10.9[b,c]	14.9±10.6	13.2±10.6	<0.001[µ]
Urinary Ca (mg/day)	-	246.5±72	415±221.5	<0.001[µ]
Urinary Cr (mg/day)	-	1171.5±399.2	1351±927.7	0.371[µ]
Ca/P	2.9±0.4[b,c]	4.1±0.9	4.6±1.1	<0.001[µ]
PTH/VitD	4.6±3.7[b,c]	17.5±17.9[c]	29.4±34.7	<0.001[µ]
PFI	13.5±7.2[b,c]	51.5±27[c]	89.4±76.2	<0.001[µ]
PTH*Ca/Vit D	43.4±34.6[b,c]	189.4±192.4[c]	325.3±387.4	<0.001[µ]
WIN	131.9±58.2[b,c]	400.7±165.9[c]	618.2±414.5	<0.001[µ]

Data presented as mean ± SD. [&]: One-way ANOVA, [µ]: Kruskal -Wallis test.
[a] There was a significant difference compared with the normal group in post-hoc comparison.
[b] There was a significant difference compared with the unoperated group in post-hoc comparison.
[c] There was a significant difference compared with the operated group in post-hoc comparison.
Ca: Calcium, P: Phosphorus, Cr: Creatinine, PTH: Parathyroid hormone, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-VitD ratio, WIN: Wisconsin index, SD: Standard deviation, PHPT: Primary hyperparathyroidism

Table 2. Comparison of laboratory parameters of the PHPT group without a surgical indication and the PHPT group that underwent surgery for osteoporosis or nephrolithiasis

	Unoperated group (n=68)	Operated group for osteoporosis (n=174)	p	Unoperated group (n=68)	Operated group for kidney stones (n=105)	p
Age (years)	60.4±7	58.6±11	0.012[&]	60.4±7	55.6±12.4	0.010[&]
Ca (mg/dL)	10.8±0.4	11±0.4	<0.001[µ]	10.8±0.4	11±0.4	<0.001[µ]
P (mg/dL)	2.7±0.5	2.5±0.5	0.140[&]	2.7±0.5	2.5±0.5	0.002[&]
Cr (mg/dL)	0.8±0.2	0.7±0.2	<0.001[µ]	0.8±0.2	1.6±8.2	0.444[µ]
PTH (pg/mL)	148.3±60.7	249±165.7	<0.001[µ]	148.3±60.7	220±133.2	<0.001[µ]
25-OH-VitD (ng/mL)	14.9±10.6	13.4±11.3	<0.001[µ]	14.9±10.6	12.6±7.6	0.353[µ]
Urinary Ca (mg/day)	246.5±72	402±233.1	<0.001[&]	246.5±72	426±202.7	<0.001[&]
Ca/P	4.1±0.9	4.6±1.1	<0.001[µ]	4.1±0.9	4.7±1.3	0.001[µ]
PTH/VitD	17.5±17.9	34.6±41.5	<0.001[µ]	17.5±17.9	27.1±29.8	0.016[µ]
PFI	51.5±27	100.6±87.9	<0.001[µ]	51.5±27	89.6±68.6	<0.001[µ]
PTH*Ca/Vit D	189.4±192.4	382.4±463.2	<0.001[µ]	189.4±192.4	299.3±326.6	0.011[µ]
WIN	400.7±165.9	687.7±466.1	<0.001[µ]	400.7±165.9	607±367.9	<0.001[µ]

Data presented as mean ± SD. [&]: Student's t-test, [µ]: Mann-Whitney U test. Ca: Calcium, P: Phosphorus, Cr: Creatinine, PTH: Parathyroid hormone, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-Vit D ratio, WIN: Wisconsin index

during the 5-year follow-up of patients with PHPT who underwent surgery, vertebral fractures developed in patients who did not undergo surgery; however, no significant difference was found between the two groups. Risk factors for fracture development include advanced age, low BMD, low 25-OH-Vit D levels, high bone turnover markers, and high PTH levels (4,17). In our study, a statistically significant relationship was found in all laboratory parameters except serum P levels in the PHPT group with osteoporosis compared with the PHPT group without surgical indications. In the ROC analysis, a WIN value of 283.2 had a sensitivity of 95% and a specificity of 72% in predicting osteoporosis, and it was identified as an independent risk factor in the regression analysis. In the study by Reid et al. (18), no independent risk factor could be detected in the analysis between laboratory values and low BMD among patients with PHPT. Although WIN was found to be an independent risk factor, no independent risk factors among laboratory parameters such as Ca, P, and PTH were associated with the variability of these values, and indices obtained from these values were considered more decisive parameters.

PHPT causes complications in the kidneys such as nephrolithiasis (prevalence, 10-20%), hypercalciuria, and GFR decline (prevalence, 15-17%) (4,8). Although a decrease in the new onset of kidney stones was observed with parathyroid surgery, nephrocalcinosis and renal failure persisted (13,19). Huang et al. (20) stated that the recurrence of nephrolithiasis despite parathyroidectomy is an important problem. The development of nephrolithiasis was associated with young age, male sex, high plasma Ca and PTH levels, a lower plasma P level, and hypercalciuria grade (18). Marchini et al. (21) revealed that the development of renal calculi in patients with PHPT was associated with serum PTH and Ca levels. In this study, the serum P level was significantly lower and although no significant difference was found in serum Cr and 25-OH-VitD levels, other laboratory parameters were significantly higher in patients with nephrolithiasis compared with the group without surgical indications. In the ROC analysis of indices that could predict the development of nephrolithiasis, the cut-off value of 36.43 for the PFIndex had a sensitivity of 86% and a specificity of 68%. However, no independent risk factor was detected in the regression analysis.

Complications develop in the long term in 25% of patients with PHPT in whom surgical treatment is not required (22). Untreated disease can sometimes silently progress with bone demineralization and increased calcium load in tissues until complications arise. Moreover, an increase in FGF-23 levels in PHPT has negative effects on the skeletal, renal, and cardiovascular systems (13). Therefore, when patients with asymptomatic PHPT should be referred for parathyroid surgery, there is still a matter of debate. For reasons such as the progression of renal failure and nephrocalcinosis after parathyroid surgery and the further occurrence of vertebral fractures in patients who do not undergo surgery, it is important to refer these patients for surgery before the development of complications. Given their high sensitivity and specificity, the WIN value of 283.2 and the PFIndex value of 36.43 can be appropriately used as surgical indications in patients with PHPT in whom osteoporosis and nephrolithiasis have not yet developed, respectively. Patients whose values are below these levels may be followed up with these parameters without performing BMD or renal US, with the advantage of low costs.

Study Limitations

This study has some limitations. Firstly, it was a retrospective study, and the number of patients without surgical indications was low. Secondly, it was impossible to obtain laboratory parameters in patients just before and after the development of complications. Therefore, the

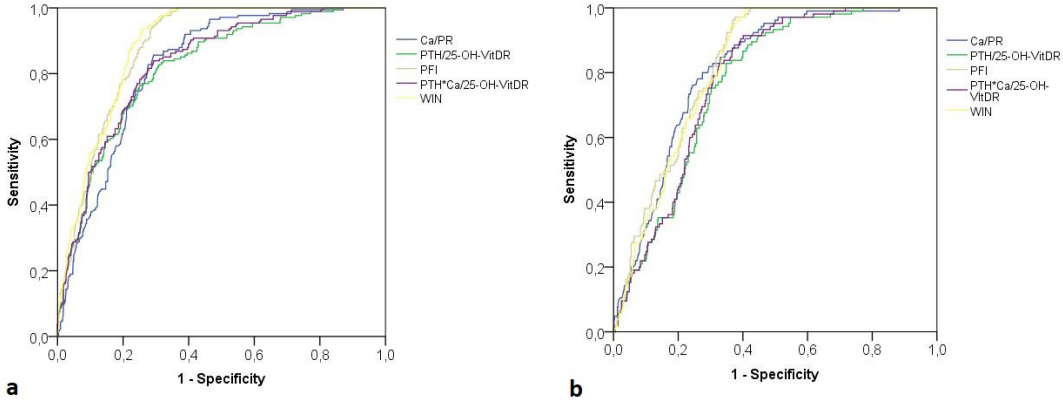

Figure 1. ROC curve analysis for indices that can predict the development of osteoporosis and nephrolithiasis
ROC: Receiver operating characteristic

Table 3. Receiver operating characteristics curve analyses of patients with osteoporosis or nephrolithiasis							
Osteoporosis							
	AUC	**SD**	**p**	**95% CI**	**Cut-off value**	**Sensitivity %**	**Specificity %**
Ca/P	0.822	0.015	<0.001	0.793-0.852	3.49	87%	68%
PTH/VitD	0.818	0.017	<0.001	0.785-0.851	13.11	82%	70%
PFI	0.879	0.011	<0.001	0.857-0.902	35.63	90%	74%
PTH*Ca/VitD	0.829	0.016	<0.001	0.798-0.861	70.93	87%	64%
WIN	0.886	0.011	<0.001	0.864-0.908	283.29	95%	72%
Nephrolithiasis							
	AUC	**SD**	**p**	**95% CI**	**Cut-off value**	**Sensitivity %**	**Specificity %**
Ca/P	0.812	0.018	<0.001	0.777-0.847	3.79	82%	70%
PTH/VitD	0.767	0.019	<0.001	0.729-0.805	8.68	83%	65%
PFI	0.825	0.016	<0.001	0.794-0.855	36.43	86%	68%
PTH*Ca/VitD	0.779	0.018	<0.001	0.743-0.815	96.33	82%	68%
WIN	0.818	0.016	<0.001	0.787-0.849	299.12	84%	67%

AUC: Area under the curve, SD: Standard deviation, CI: Confidence interval, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-VitD ratio, WIN: Wisconsin index

Table 4. Multivariate and univariate logistic regression analyses of parameters effective in predicting osteoporosis in patients with PHPT								
	Multivariate				**Univariate**			
	B	**p**	**OR**	**95% CI**	**B**	**p**	**OR**	**95% CI**
Ca/P	0.300	0.371	1.35	0.70-2.60	0.507	0.002	1.66	1.21-2.28
PTH/VitD	0.201	0.192	0.82	0.61-1.11	0.025	0.002	1.03	1.01-1.04
PFI	0.018	0.401	0.98	0.94-1.02	0.024	<0.001	1.02	1.01-1.04
PTH*Ca/VitD	0.017	0.224	1.02	0.99-1.05	0.002	0.002	1.00	1.00-1.01
WIN	0.007	0.031	1.51	1.01-1.71	0.004	<0.001	1.58	1.00-1.81

OR: Odds ratio, CI: Confidence interval, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-Vit D ratio, WIN: Wisconsin index, PHPT: Primary hyperparathyroidism

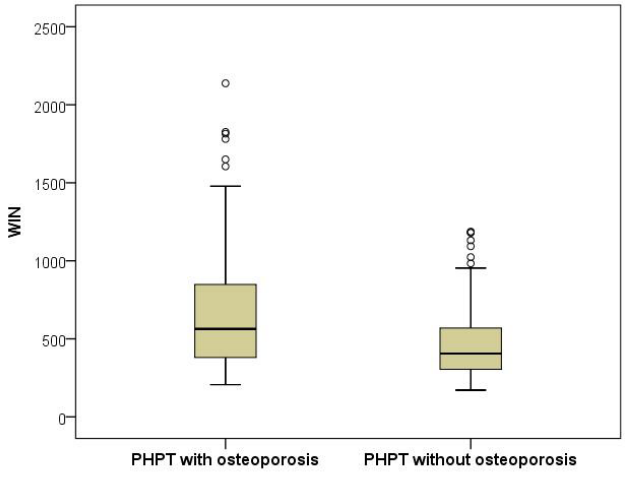

Figure 2. WIN results of patients with PHPT who were operated for osteoporosis and patients with PHPT who did not have an operation indication
WIN: Wisconsin index, PHPT: Primary hyperparathyroidism

values of patients at the time of presentation were used in the study. However, our study is important because it is the first study to identify an independent predictor of osteoporosis and present a cut-off value with relatively high sensitivity and specificity values for the presence of both osteoporosis and nephrolithiasis.

Conclusion

In our study, it has been shown that WIN and PFIndex can properly predict the presence of nephrolithiasis and osteoporosis. WIN can be used specifically as an independent predictor of osteoporosis. With these results, low-risk patients according to WIN and PFIndex may be followed up with routine blood tests and urinary Ca excretion, whereas BMD and renal US may be reserved for high-risk patients. WIN and PFIndex can be calculated with routine blood tests for PHPT, and no extra cost is required. With these indices, low-risk patients are detected, and there is no additional cost and time loss for renal US and BMD. Our findings should be supported by further prospective studies, including larger sample sizes.

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Ethics

Ethics Committee Approval: This study was approved by the local ethics committee of Yozgat Bozok University, Faculty of Medicine (Ethics Committee no: 2017-KAEK-189_2020.10.14_01).

Informed Consent: This multicenter retrospective cross-sectional study.

Authorship Contributions

Concept: O.O.B., D.K., Z.C., M.C., Design: O.O.B., Data Collection and/or Processing: O.O.B., D.K., Z.C., Analysis and/or Interpretation: O.O.B., Literature Research: O.O.B., Writing: O.O.B., D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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