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Table 1: Demographics, biomarker levels and imaging parameters in CKD patients and control participants.

Variables	CKD (N=69)	Control (N=68)	p values
Age, years	62 (12)	62 (12)	
Male, N	53	53	
BMI (kg/m^2)	27 (4.1)	28 (4.3)	0.3
Diabetes	28%	0%	**<0.001**
Previous fragility fracture	22%	7%	**<0.05**
Biochemical markers			
iPTH (pg/mL)	188 (121 – 280)	32 (27 – 45)	**<0.001**
Intact PINP (ng/mL)	67.5 (42.8 – 107.7)	38.5 (31.8 – 55.3)	**<0.001**
Total PINP (ng/mL)	125 (72.8 – 237.2)	41.4 (33.7 – 56.7)	**<0.001**
bALP (µg/L)	22.3 (16.6 – 33.3)	17 (12.9 – 20.2)	**<0.001**
tALP (IU/L)	88 (73 – 126)	65.5 (55.3 – 78)	**<0.001**
CTX (ng/mL)	1.49 (0.76 – 2.39)	0.27 (0.19 – 0.5)	**<0.001**
TRAP5b (U/L)	4.9 (3.2 – 6.9)	3.8 (3.3 – 4.5)	**0.001**
Adjusted calcium (mmol/L)	2.28 (0.15)	2.28 (0.07)	0.9
Phosphate (mmol/L)	1.53 (0.3)	1.06 (0.15)	**<0.001**
25-hydroxyvitamin D (ng/mL)	22.9 (9.4)	23.9 (7.0)	0.5
HRpQCT distal radius			
Total vBMD (mg/cm^3)	266.2 (75.56)	308.47 (74.2)	**0.003**
Cortical vBMD (mg/cm^3)	782.58 (110.66)	821.04 (88.7)	**0.04**
Trabecular vBMD (mg/cm^3)	156.69 (46.17)	184.6 (41.42)	**0.001**
Cortical thickness (mm)	0.61 (0.27)	0.71 (0.26)	0.06
Cortical porosity (%)	3.0 (2.3 – 4.2)	3.2 (2.0 – 3.8)	0.4
Cortical BV/TV (%)	90.0 (85.4 – 92.1)	90.7 (88.6 – 93.4)	0.1
Trabecular thickness (mm)	0.064 (0.012)	0.073 (0.013)	**<0.001**
Trabecular number (1/mm)	2.01 (0.363)	2.11 (0.296)	0.14
Trabecular separation (mm)	0.434 (0.371 – 0.496)	0.4 (0.349 – 0.443)	0.06
Trabecular BV/TV (%)	13.1 (3.8)	15.4 (3.5)	**0.001**
HRpQCT distal tibia			
Total vBMD (mg/cm^3)	276.99 (63.67)	314.97 (61.2)	**0.001**
Cortical vBMD (mg/cm^3)	819.85 (88.67)	858.7 (67.89)	**0.005**
Trabecular vBMD (mg/cm^3)	172.12 (41.06)	189.99 (41.12)	**0.01**
Cortical thickness (mm)	1.05 (0.36)	1.25 (0.35)	**0.001**
Cortical porosity (%)	7.1 (5.7 – 10.4)	6.8 (4.7 – 10.3)	0.2
Cortical BV/TV (%)	86.2 (6.0)	88.1 (4.9)	0.05
Trabecular thickness (mm)	0.075 (0.014)	0.081 (0.013)	**0.01**
Trabecular number (1/mm)	1.92 (0.35)	1.97 (0.4)	0.4
Trabecular separation (mm)	0.444 (0.395 – 0.522)	0.425 (0.359 – 0.523)	0.2
Trabecular BV/TV (%)	14.3 (3.4)	15.8 (3.4)	**0.01**
DXA BMD Z-score			
Forearm	-0.4 (1.5)	0.2 (1.4)	**0.02**
Total hip	-0.2 (1.0)	0.6 (1.1)	**<0.001**

Lumbar spine	0.4 (1.7)	0.5 (1.6)	0.7

Data presented as mean (standard deviation) for normal distribution variables and median (inter-quartile range) for non-normal distribution variables. Group differences were tested using independent t-test for normal distribution variables, Mann-Whitney U test for non-normal distribution variables and chi squared test for categorical variables.

Abbreviations: eGFR; estimated glomerular filtration rate; BMI, body mass index; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal; bALP, bone alkaline phosphatase; tALP, total alkaline phosphatase CTX, collagen type 1 cross-linked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b; HR-pQCT, high resolution peripheral quantitative computed tomography; vBMD, volumetric bone mineral density; BV/TV, bone volume/tissue volume; DXA, dual energy X-ray absorptiometry; BMD, bone mineral density.

Table 2: Biomarkers and imaging parameters for low, normal and high bone turnover categories in advanced chronic kidney disease patients (N=43).

Variables	Low (N=11)	Normal (N=15)	High (N=17)	p value
BFR/BS (um3/um2/day)	13.8 (3.6 – 15.5)	27.5 (22.5 – 32.2)	67.4 (46.5 – 112.5)	**<0.001**
Medications				
Vitamin D	45%	13%	47%	
Calcium based phosphate binder	9%	20%	41%	
Non-Calcium based phosphate binder	0%	7%	6%	
Biochemistry				
iPTH (pg/mL)	172 (119 – 292)	172 (86 – 194)	347 (161 – 381)	**<0.05**
Intact PINP (ng/mL)	44.1 (29.2 -68.4)	81.1 (54.3 – 92.4)	107.9 (63.5 – 182)	**<0.005**
Total PINP (ng/mL)	76.3 (51.7 – 159.3)	127.3 (68.4 – 221.7)	214 (110.6 – 403)	**<0.05**
bALP (µg/L)	17.7 (5.6)	25.9 (8.7)	34.4 (13.3)	**<0.005**
tALP (IU/L)	82 (53 – 86)	94 (82 – 127)	115 (82 – 156)	**<0.05**
CTX (ng/mL)	1.01 (0.68)	1.46 (0.67)	2.65 (1.68)	**<0.005**
TRAP5b (U/L)	3.2 (2.9 – 4.3)	5.2 (3.2 – 7.4)	5.8 (4.8 – 8.5)	**<0.05**
Adjusted calcium (mmol/L)	2.27 (2.22 – 2.33)	2.32 (2.26 – 2.35)	2.24 (2.14 – 2.40)	0.6
Phosphate (mmol/L)	1.48 (1.30 – 1.77)	1.61 (1.43 – 1.83)	1.30 (1.25 – 1.55)	0.1
25-hydroxyvitamin D (ng/mL)	23 (9.9)	23.7 (8.2)	22.6 (10.3)	0.95
HR-pQCT radius Z-score				
Total vBMD	-0.11 (0.63)	-1.06 (0.66)	-0.97 (1.08)	**<0.05**
Cortical vBMD	0.49 (-0.47 to 0.9)	-0.63 (-1.4 to -0.14)	-0.84 (-1.67 to 0.15)	0.09
Trabecular vBMD	-0.31 (0.83)	-1.03 (0.57)	-1.11 (1.31)	0.16
Cortical thickness	0.07 (0.8)	-0.76 (0.82)	-0.64 (0.98)	0.1
Cortical porosity	-0.51 (-0.95 to -0.02)	-0.12 (-0.94 to 1.58)	0.10 (-0.47 to 0.90)	0.15
Cortical BV/TV	0.72 (-0.08 to 0.97)	-0.2 (-1.48 to 0.27)	-0.23 (-1.46 to 0.27)	**<0.05**
Trabecular thickness	-0.43 (-0.82 to -0.18)	-1.14 (-1.57 to -0.79)	-1.21 (-1.77 to 0.11)	0.07
Trabecular number	-0.03 (1.01)	-0.11 (0.84)	-0.66 (1.58)	0.39
Trabecular separation	-0.13 (-0.5 to 0.71)	0.30 (-0.39 to 0.55)	0.59 (-0.50 to 1.18)	0.5
Trabecular BV/TV	-0.30 (0.82)	-1.01 (0.57)	-1.09 (1.31)	0.17
HR-pQCT tibia Z-score				
Total vBMD	-0.34 (0.91)	-1.05 (0.90)	-0.92 (1.13)	0.21
Cortical vBMD	0.26 (-0.93 to 0.44)	-0.60 (-2.0 to 0.31)	-0.21 (-2.0 to 0.13)	0.13
Trabecular vBMD	-0.48 (0.92)	-0.63 (0.88)	-0.70 (1.11)	0.86
Cortical thickness	-0.18 (0.92)	-1.1 (0.86)	-0.86 (1.16)	0.1
Cortical porosity	-0.31 (0.52)	0.43 (1.26)	0.31 (1.17)	0.23
Cortical BV/TV	0.36 (-0.15 to 0.73)	-0.43 (-1.82 to 0.70)	0.14 (-2.12 to 0.37)	0.17
Trabecular thickness	-0.70 (-0.87 to 0.23)	-0.93 (-1.62 to 0.21)	-0.78 (-1.66 to 0.14)	0.44
Trabecular number	-0.31 (1.23)	-0.03 (0.76)	-0.07 (0.92)	0.74
Trabecular separation	0.56 (-0.75 to 0.84)	-0.09 (-0.30 to 0.55)	-0.04 (-0.44 to 0.52)	0.66
Trabecular BV/TV	-0.46 (0.91)	-0.60 (0.88)	-0.67 (1.10)	0.86
DXA BMD Z-score				
Forearm	-0.24 (0.88)	-0.31 (0.99)	-0.94 (1.33)	0.18

Total hip	-0.07 (0.76)	-0.35 (0.96)	-0.38 (1.05)	0.68
Lumbar spine	-0.10 (-0.5 to 0.6)	0.2 (-0.8 to 1.0)	0 (-0.8 to 1.3)	0.86

Data is presented as mean (standard deviation) for normal distribution variables or median (interquartile range) for non-normal distribution variables. Group differences were tested using one-way ANOVA or Kruskal-Wallis test depending on the distribution of the variables.

Abbreviations: BFR/BS, bone formation rate/bone surface; eGFR; estimated glomerular filtration rate; BMI, body mass index; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal; bALP, bone alkaline phospahatse; tALP, total alkaline phosphatase; CTX, collagen type 1 cross-linked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b; HR-pQCT, high resolution peripheral quantitative computed tomography; vBMD, volumetric bone mineral density; BV/TV, bone volume/tissue volume; DXA, dual energy X-ray absorptiometry; BMD, bone mineral density.

Table 3: Diagnostic accuracy of bone turnover markers, radius HR-pQCT and combined variables for identifying patients with low bone turnover

Variables	AUC (95% CI)	Criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BTMs						
iPTH	0.563 (0.401 to 0.715)	≤183 pg/mL	70	53	32	85
Intact PINP	0.794 (0.641 to 0.903)	≤57 ng/mL	80	75	50	92
Total PINP	0.719 (0.557 to 0.848)	≤124 ng/mL	80	68	44	91
bALP	0.824 (0.671 to 0.926)	≤21 µg/L	89	77	53	96
tALP	0.753 (0.598 to 0.871)	≤88 IU/L	91	63	46	95
CTX	0.766 (0.610 to 0.882)	≤0.84 ng/mL	60	84	55	87
TRAP5b	0.799 (0.643 to 0.909)	≤4.6 U/L	89	71	47	96
Radius HR-pQCT Z-score						
Total vBMD	0.811 (0.646 – 0.922)	>-1.0	100	59	45	100
Cortical BV/TV	0.802 (0.636 – 0.916)	> -0.2	89	63	44	94
Combined variables						
bALP & radius total vBMD Z-score	0.797 (0.621 – 0.916)	Not available	100	58	39	100

Abbreviations: BTMs, bone turnover markers; HR-pQCT, high resolution peripheral quantitative computed tomography; AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal peptide ; bALP, bone alkaline phosphatase; tALP, total alkaline phosphatase; CTX, collagen type 1 cross-linked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b; vBMD, volumetric bone mineral density; BV/TV, bone volume/tissue volume.

Table 4: Diagnostic accuracy of bone turnover markers for identifying patients with high bone turnover.

Bone turnover markers	AUC (95% CI)	Criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
iPTH	0.760 (0.603 to 0.878)	>327 pg/mL	53	96	90	75
Intact PINP	0.765 (0.609 to 0.882)	>107 ng/mL	53	92	82	74
Total PINP	0.725 (0.563 to 0.853)	>142ng/mL	75	68	60	81
bALP	0.750 (0.588 to 0.873)	>31 µg/L	56	83	69	74
tALP	0.670 (0.510 to 0.805)	>102 IU/L	65	73	61	76
CTX	0.762 (0.606 to 0.880)	>2.39 ng/mL	53	96	90	75
TRAP5b	0.710 (0.545 to 0.842)	>4.6 U/L	81	58	57	82

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal peptide ; bALP, bone alkaline phosphatase; tALP, total alkaline phosphatase; CTX, collagen type 1 cross-linked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b.

Supplementary Table 1: Correlation between all bone turnover markers in 43 advanced CKD patients with bone histomorphometry data.

	Intact PINP	Total PINP	bALP	tALP	CTX	TRAP5b
iPTH	0.619	0.523	0.621	0.508	0.567	0.504
Intact PINP		0.813	0.866	0.762	0.732	0.741
Total PINP			0.749	0.698	0.591	0.575
bALP				0.869	0.710	0.672
tALP					0.542	0.548
CTX						0.709

All Spearman's rho correlations are significant at ≤0.001 (2-tailed)

Supplementary Table 2: Diagnostic accuracy of DXA areal BMD Z-scores for identifying advanced CKD patients with low and high bone turnover (N=43).

Areal BMD Z-score	AUC (95% CI)
Low bone turnover	
Forearm	0.645 (0.483 – 0.786)
Total hip	0.598 (0.438 – 0.744)
Lumbar spine	0.554 (0.395 – 0.705)
High bone turnover	
Forearm	0.685 (0.523 – 0.819)
Total hip	0.580 (0.420 – 0.729)
Lumbar spine	0.533 (0.375 – 0.686)

Supplementary Table 3: Diagnostic accuracy of HR-pQCT Z-scores for identifying advanced CKD patients with high bone turnover (N=43).

| HR-pQCT Z-scores	Distal radius AUC (95% CI)	Distal tibia AUC (95% CI)
Total vBMD	0.627 (0.450 – 0.782)	0.553 (0.392 – 0.706)
Cortical vBMD	0.569 (0.394 – 0.732)	0.579 (0.417 – 0.729)
Trabecular vBMD	0.625 (0.448 – 0.780)	0.541 (0.381 – 0.696)
Cortical thickness	0.552 (0.377 – 0.717)	0.525 (0.365 – 0.681)
Cortical porosity	0.627 (0.450 – 0.782)	0.548 (0.387 – 0.702)
Cortical BV/TV	0.628 (0.451 – 0.783)	0.576 (0.414 – 0.727)
Trabecular thickness	0.583 (0.407 – 0.744)	0.575 (0.413 – 0.726)
Trabecular number	0.603 (0.427 – 0.762)	0.541 (0.381 – 0.696)
Trabecular separation	0.614 (0.438 – 0.771)	0.533 (0.373 – 0.688)
Trabecular BV/TV	0.628 (0.451 – 0.783)	0.542 (0.382 – 0.697)

Figure 1: Examples of HR-pQCT 3-dimensional images of distal radius and distal tibia from a control participant and a CKD patient in this study.
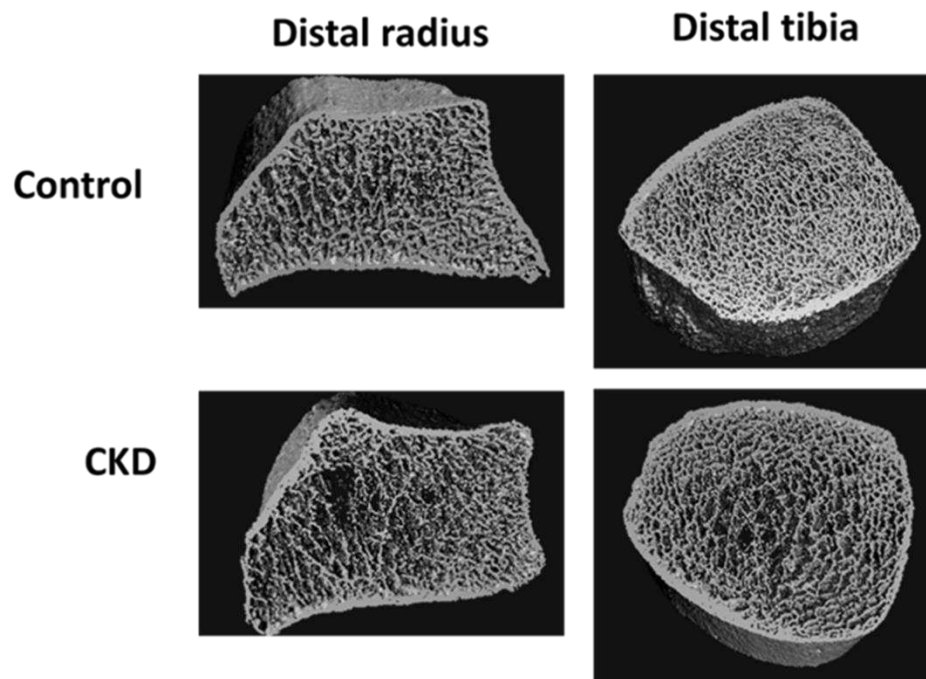
Figure 2: Correlations between bone turnover (BFR/BS) on bone histomorphometry and bone turnover markers (N=43).
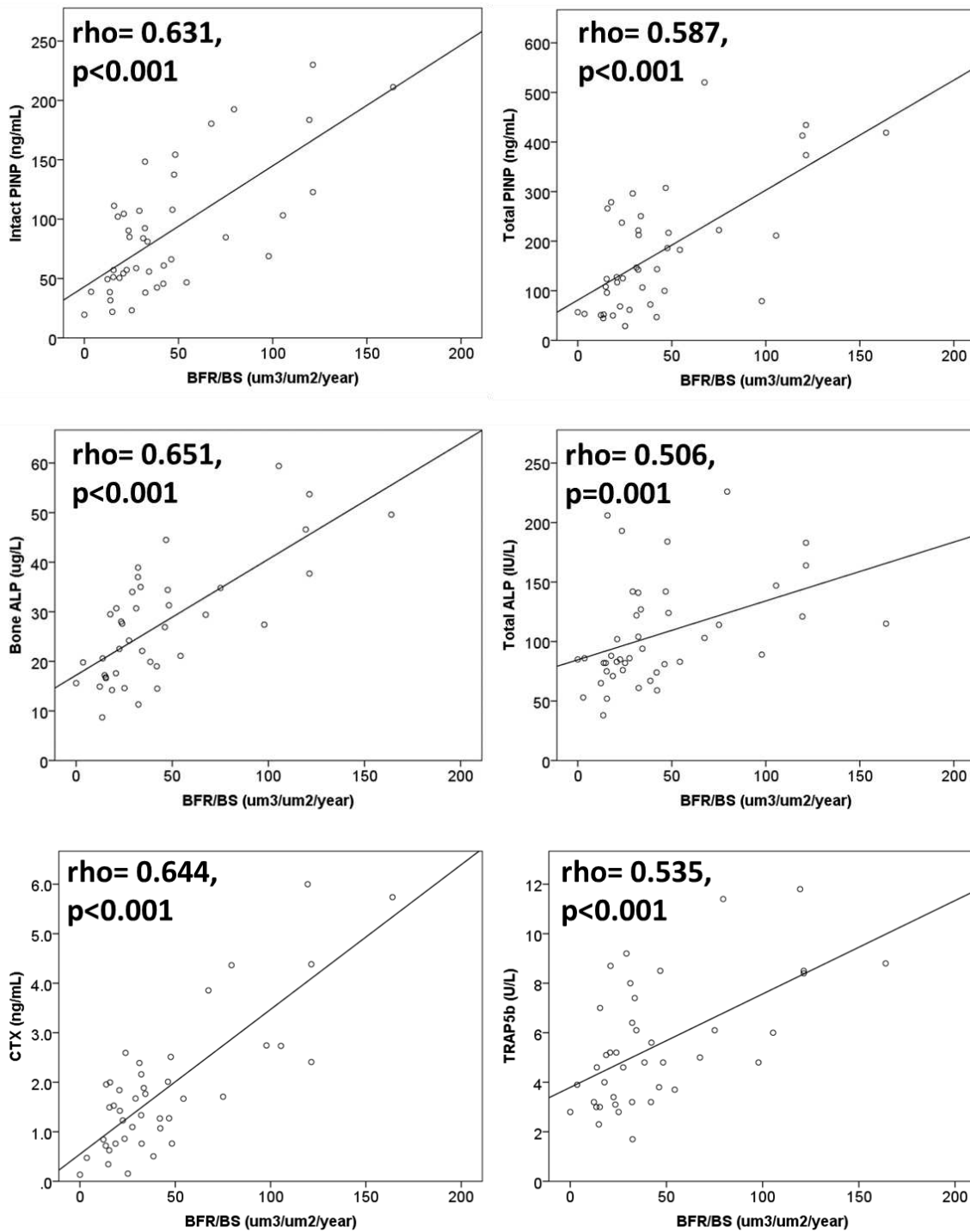
Figure 3: Associations between bone turnover (BFR/BS) on bone histomorphometry and radius HR-pQCT parameters (n=43)
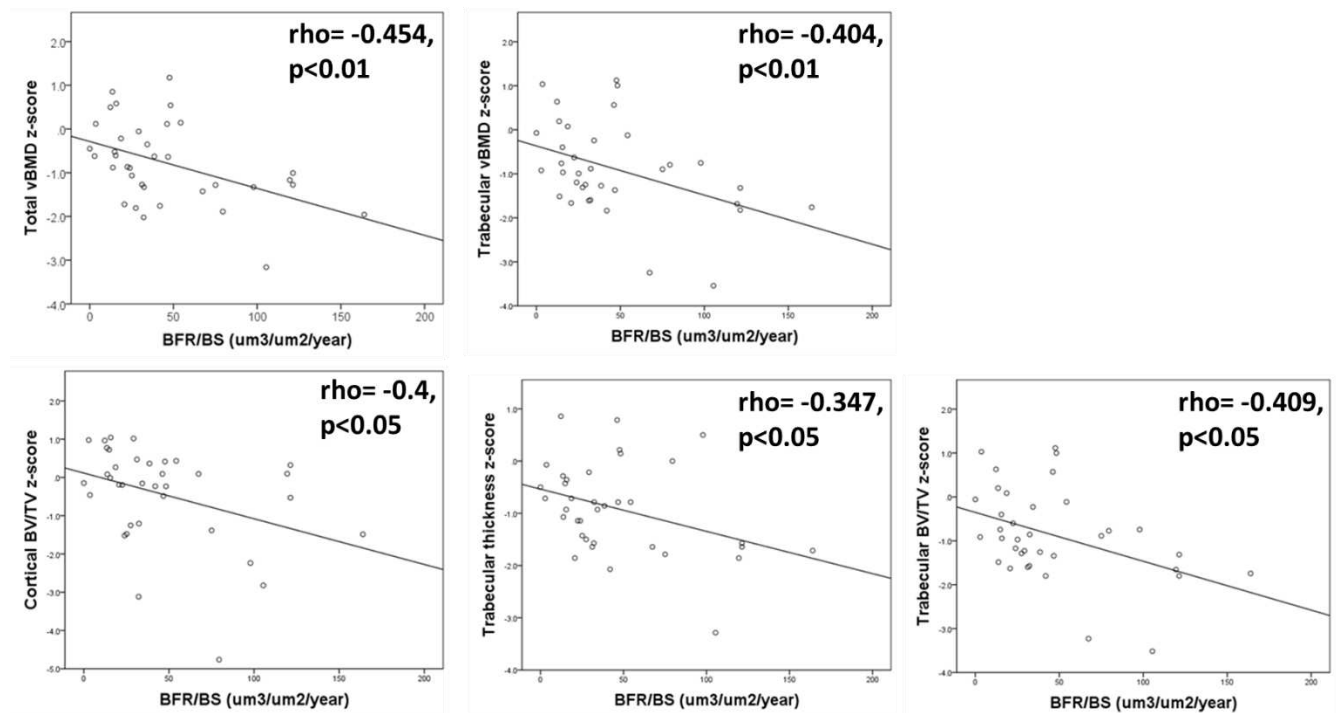
Figure 4: Receiver operating characteristic (ROC) curves for (A) BTMs and (B) radius HR-pQCT parameters for identifying CKD patients with low bone turnover.