

Research Article

Diagnostic Value of I-131 NP-59 SPECT/CT Scintigraphy in Patients with Subclinical or Atypical Features of Primary Aldosteronism

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Accumulating evidence has shown the adverse effect of long-term hyperaldosteronism on cardiovascular morbidity that is independent of blood pressure. However, the diagnosis of primary aldosteronism (PA) remains a challenge for patients who present with subtle or atypical features or have chronic kidney disease (CKD). SPECT/CT has proven valuable in the diagnosis of a number of conditions. The aim of this study was to determine the usefulness of I-131 NP-59 SPECT/CT in patients with atypical presentations of PA and in those with CKD. The records of 15 patients with PA were retrospectively analyzed. NP-59 SPECT/CT was able to identify adrenal lesion(s) in CKD patients with suspected PA. Patients using NP-59 SPECT/CT imaging, compared with those not performing this procedure, significantly featured nearly normal serum potassium levels, normal aldosterone-renin ratio, and smaller adrenal size on CT and pathological examination and tended to feature stage 1 hypertension and non-suppressed plasma renin activity. These findings show that noninvasive NP-59 SPECT/CT is a useful tool for diagnosis in patients with subclinical or atypical features of PA and those with CKD.

1. Introduction

Primary aldosteronism (PA) is the most common cause of surgically curable secondary hypertension and affects more than 10% of the general hypertensive population [1]. Stage 2 hypertension according to the Seventh Joint National Committee (JNC 7) [2] with or without symptomatic hypokalemia leads to a higher probability of PA detection, and the diagnostic approach is straightforward in three steps: case-finding screening testing of elevated plasma aldosterone concentration (PAC), suppressed plasma renin activity

(PRA), and a high aldosterone to renin ratio (ARR), followed by aldosterone suppression confirmatory testing and subtype studies of computed tomography (CT) imaging, adrenal vein sampling, or I-6-beta-iodomethylnorcholesterol (I-131 NP-59) scintigraphy. However, normotensive PA patients, featured as elevated PAC, have been reported [3], and the ARR is not reliable in patients with chronic kidney disease (CKD) [4]. Therefore, diagnosing PA can be tricky when clinical and biochemical features vary widely and the criteria for PA cannot be met, especially in patients with CKD or who present with subclinical symptoms featured as

stage 1 hypertension or are found to have atypical laboratory testing.

It has been reported that an increased serum aldosterone level in normotensive individuals leads to the development of sustained hypertension in the future [5]. Moreover, patients with PA are at greater risk than those with the same degree of blood pressure (BP) but without PA for cardiovascular events and stroke because long-term hyperaldosteronism leads to vessel and heart damage that is independent of BP [6]. Therefore, normalization of circulating aldosterone is the paramount therapeutic goal for PA [7], and timely identification of subclinical or atypical features of PA is of clinical value.

The common modalities used for subtype identification of PA also have limitations. Adrenal CT scan is considered the initial diagnostic modality for the identification of adrenal nodules; however, its diagnostic sensitivity is estimated to be 50% [8]. Adrenal CT imaging cannot correctly detect adrenal microadenoma smaller than 1 cm in diameter and bilateral adrenal hyperplasia, both of which may present normal-appearing adrenals. Adrenal vein sampling is the diagnosis of choice to differentiate unilateral from bilateral disease in patients with PA; however, this technique is invasive and difficult to access the right adrenal vein [9] and inevitably carries some risk of adrenal hemorrhage [10], despite being performed by an experienced radiologist. Moreover, it appears to be rarely applied to patients with CKD and an increased bleeding tendency. Dexamethasone-suppression NP-59 scintigraphy has a high affinity for adrenocortical tissue, but traditional planar imaging has low sensitivity and specificity for detection of early adrenal activity, especially adenoma smaller than 1 cm in diameter [11]. Therefore, diagnosis can be challenging in patients who have CKD or/and present with subclinical symptoms or/and are found to have atypical laboratory testing or/and negative imaging studies.

Single photon emission computed tomography (SPECT)/CT imaging is a significant technical innovation that simultaneously provides anatomic and functional information to allow for better localization of tracer activity and to enhance diagnostic accuracy and sensitivity [12]. SPECT/CT has proven valuable in oncology and neurology [13] and has the advantage of identifying small lesions demonstrated in several case reports of nephrology [14, 15]. Recently, I-131 NP-59 SPECT/CT has been recommended as a diagnostic method of choice for patients with clinically confirmed PA, but inclusive CT or adrenal vein sampling results, because of its high sensitivity (up to 81.8%) and diagnostic accuracy [16]. To the best of our knowledge, there has been no clinical study of the use of NP-59 SPECT/CT in patients with subclinical or atypical PA or CKD patients with suspected PA. Thus, this aim of this study was to determine the usefulness of I-131 NP-59 SPECT/CT in patients with atypical presentations of PA and in those with CKD.

2. Materials and Methods

2.1. Patients. The records of 14 patients with PA (5 males, 10 females) with a median age of 55.9 years (range,

27–72 years) who underwent adrenalectomy at our institution from April 2007 to April 2010 were retrospectively reviewed. Patients were followed until October 2010. One patient who did not undergo adrenalectomy because of clinically confirmed bilateral adrenal hyperplasia was also included in the analysis. Therefore, the study included 15 patients, 14 with pathologically confirmed PA, and one with clinically confirmed PA. Of the 15 patients, 6 who received NP-59 SPECT/CT imaging served as the SPECT/CT group, and the other 9 who did not receive NP-59 SPECT/CT imaging served as the control group. The complete data of these 15 patients are presented in Tables 1 and 2 and summarized in Figure 1. The median period of followup was 216 days (range: 183–527 days). The study was approved by our Institutional Review Board.

2.2. Data Collection. We collected clinical data including age, gender, systolic and diastolic BP at admission, chief complaints, laboratory results (serum potassium [K], plasma aldosterone concentration [PAC], plasma renin activity [PRA], aldosterone-renin-ratio [ARR], and transtubular potassium gradient [TTKG]) or 24-hour urinary potassium excretion, and confirmatory tests results (including saline loading test or/and captopril test) if done, followup outcomes, and imaging and pathological data. PAC and PRA were measured by commercial RIA kits (ALDOCTK, #P2714, Diasorin Inc., MN, USA, and GAMMACOAT PLASMA RENIN ACTIVITY, #CA-1533, Diasorin Inc., MN, USA, resp.). Normal ranges for PAC and PRA are 3.7–24 ng/dL and 0.15–2.33 ng/mL/h, respectively.

2.3. Definitions. The definition of hypertension stage was based on the JNC 7 classifications [2], that is, stage 1 hypertension was defined as a BP of 140/90 mm Hg or greater, and stage 2 hypertension was defined as a BP of 160/100 mm Hg or greater. A positive captopril test was defined as PAC suppression >30% after oral administration of 25 mg of captopril, taken 2 hours before sampling [17]. A positive saline loading test was defined as PAC > 10 ng/dL after intravenous infusion of 2 L of 0.9% saline over 4 h [17]. An ARR > 30 was considered to be positive [10]. All drugs that can affect the ARR were discontinued for 2 weeks before performing confirmatory tests. Symptomatic hypokalemia was defined as serum K < 3.0 mEq/L. A TTKG > 4 was considered positive for kaliuria. Improvement was defined as a well-controlled BP with no or a decreased dose of antihypertensive medications, and normalization or decrease of PAC, PRA, and serum K. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², based on the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines [18]. Stage 3 CKD was defined as an eGFR of 30 to 59 mL/min/1.73 m². Stage 4 was defined as an eGFR of 15 to 29 mL/min/1.73 m². Stage 5 was defined as an eGFR of less than 15 mL/min/1.73 m².

2.4. Patient Preparation and NP-59 Planar, SPECT, and SPECT/CT Imaging. A dexamethasone suppression regimen (1 mg orally 4 times daily) was initiated 7 days before

TABLE 1: Demographic and clinical data of study subjects.

Patient	Age (y)	Gender	BP (mm Hg) at admission		HTN* stage	Chief complaint	Serum K (mEq/L)	PAC# (ng/dL)	PRA# (ng/mL/h)	ARR	TTKG	Confirmatory tests	
			SBP	DBP								Test	Result
Control group (n = 9)													
1	50	F	230	130	2	HTN	2.2	60.08	0.13	462	—	Captopril	Positive
2	34	F	186	105	2	Weakness	1.6	45.80	0.13	352	4.5	Saline loading Captopril	Positive
3	58	F	220	120	2	HTN	2.69	29.28	0.13	225	—	—	Positive
4	32	F	182	121	2	HTN	2.87	40.00	1.71	23	—	—	—
5	71	F	146	94	1	Weakness	2.61	32.10	0.05	642	6.2	—	—
6	59	M	152	71	1	HTN	3.49	25.55	0.45	57	—	Saline loading	Positive
7	60	F	160	90	2	Weakness	1.74	110.70	0.18	615	11.9	—	—
8	72	M	180	117	2	Weakness	1.96	31.80	0.06	122	—	—	—
9	56	F	154	83	1	Weakness	2.76	21.70	0.53	41	6.1	—	—
SPECT/CT group (n = 6)													
10	55	F	140	90	1	Accidentally palpable Irregular pulse	3.24	31.9	2.52	13	8.8	Saline loading Captopril	Negative
11	48	F	145	80	1	HTN	4.01	26.8	0.06	447	—	Saline loading Captopril	Negative
12 [†]	57	M	170	100	2	HTN	2.79	37.2	0.32	116	72.1 mEq/d [‡]	Saline loading	Negative
13	56	M	144	90	1	—	4.14	25.3	1.31	12	—	—	—
14	39	M	206	115	2	HTN	2.2	27.5	1.68	16	8.2	—	—
15 [†]	27	F	150	88	1	HTN	4.32	29.3	1.62	18	—	Captopril	Negative

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; S/S: symptom/sign; K: potassium; PAC: plasma aldosterone concentration; PRA: plasma renin activity; ARR: aldosterone-renin ratio; TTKG: transtubular potassium gradient; F: female; M: male.

Normal range of PAC, PRA, and serum K is 3.7–24 ng/dL, 0.15–2.33 ng/mL/h, and 3.5 to 5.0 mEq/L, respectively.

* HTN stage according to JNC 7 report.

[†] Patients 12 and 15 had stages 3 and 4 chronic kidney disease with serum creatinine level of 2.2 mg/dL (eGFR 32.9 mL/min/1.73 m²) and 2.5 mg/dL (eGFR 24.6 mL/min/1.73 m²), respectively.

[‡] 24-hour urine excretion of potassium.

Screening testing and confirmatory testing		Pathology-p (n = 14)*									
		Category 1# (n = 8)				Category 2# (n = 2)		Category 3# (n = 2)		Category 4# (n = 3)	
		Control (n = 6)		SPECT/CT (n = 2)		Control (n = 2)		Control (n = 1)	SPECT/CT (n = 1)	SPECT/CT (n = 3)	
		CT-p		CT-p		CT-p		CT-p	CT-n	CT-p	CT-n
		BP-imp		BP-not		BP-imp		BP-imp		BP-imp	
PAC↑, PRA↓, ARR↑ (typical features)	test-p	Patient 2 (kaliuria) Patient 1, 3								Patient 11	
	test-n	Patient 8				Patient 5 (kaliuria)					
	test-nd							Patient 6			
PAC↑, PRA—, ARR↑	test-p	Patient 12 (stage 3 CKD) (kaliuria)									
	test-n	Patient 7 (kaliuria)									
	test-nd										
PAC↑, PRA—, ARR—	test-n	Patient 14 (kaliuria)						Patient 10 (kaliuria)		Patient 15 (stage 4 CKD) (Figure 2)	
	test-nd	Patient 4								Patient 13	
PAC—, PRA—, ARR↑						Patient 9 (kaliuria)					

Abbreviations: p, positive; n, negative; nd, not done; BP-imp, BP improve; BP-not, BP not improve; ↑, elevate; ↓, suppressed; —, within normal range; test, confirmatory test; other abbreviations are the same as Tables 1 and 2.

Arrow from left to right denotes symptoms presented from severe to mild form; arrow from up to down denotes screening testing from typical to atypical features.

*Exclude patient 15 because of bilateral adrenal hyperplasia.

#Four categories were ordered by the severity of symptoms: category 1, stage 2 hypertension and hypokalemia; category 2, stage 1 hypertension and hypokalemia; category 3, stage 1 hypertension and low-normal potassium level; category 4, stage 1 hypertension and normal potassium level.

FIGURE 1: Qualitative analysis of Tables 1 and 2.

tracer injection and this was continued throughout the imaging procedure and for 5 days postinjection [12]. Patients were also given 5 drops daily of Lugol's solution 3 days before the start of imaging to block thyroid uptake of free I-131, and This was continued until the end of the imaging period. All drugs that can interfere with NP-59 uptake were discontinued for 4 weeks before imaging [12]. NP-59 scanning was performed on days 1 through 5 to obtain planar images after intravenous injection of 1.5 mCi (56 MBq) NP-59. SPECT/CT scanning was performed on days 2 through 5 with a dural-head gamma camera (DST-XLi; GE Medical Systems, Buc, France) to obtain SPECT and merged SPECT/CT images.

2.5. Imaging Interpretation. CT images with fine cuts (3 mm) were obtained and interpreted by a well-experienced radiologist. The NP-59 planar, SPECT, and SPECT/CT images were interpreted by 2 nuclear medicine specialists. Aldosteronism on the affected side(s) was considered if there was early visualization of the tracer on imaging before the fifth postinjection day and intense uptake greater than that in the liver [12].

2.6. Adrenalectomy and Pathological Interpretation. Of the 15 patients, 14 underwent laparoscopic adrenalectomy by an

experienced surgeon. The histopathological examinations of the surgical specimens were performed by an experienced pathologist.

2.7. Statistical Analysis. All data are expressed as median (range). The differences between the SPECT/CT group and the control group were compared by Fisher's exact test for categorical variables, or by Mann-Whitney U test for continuous variables. A two-sided P value less than .05 was considered statistically significant. All data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

3. Results

Pathological examination showed that 12 of 15 patients had unilateral adenomas, 1 had a micronodule, and 1 had unilateral focal nodular hyperplasia (Table 2). 1 had clinically confirmed bilateral adrenal hyperplasia (Figure 2).

3.1. Differences of Clinical Pictures between the Control and SPECT/CT Groups (Table 1). In the control group (n = 9), 6 subjects had stage 2 hypertension along with symptomatic hypokalemia; 2 had stage 1 hypertension along with symptomatic hypokalemia; one had stage 1 hypertension

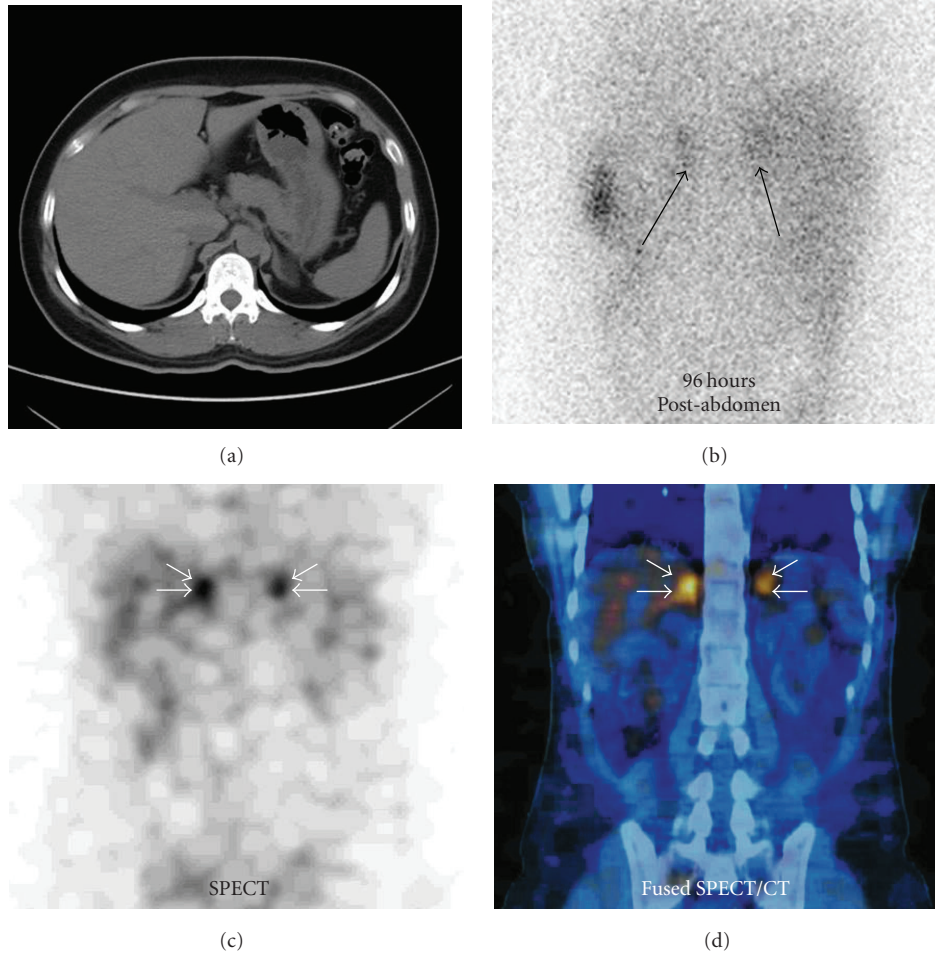


FIGURE 2: A 27-year-old woman (patient 15) who had stage 4 CKD presented with stage 1 hypertension alone due to bilateral adrenal hyperplasia, whose PAC was elevated, but whose serum potassium level was normal, whose PRA was nonsuppressive, whose ARR was negative, whose confirmatory testing was negative, whose bilateral adrenal lesions had normal appearing on CT (a) and faint uptakes on planar imaging (b) but true positive on SPECT (c) and coronal SPECT/CT (d) imaging. After treatment with 25 mg of spironolactone, her BP and PAC were normalized.

without symptomatic hypokalemia. In the SPECT/CT group ($n = 6$), 4 subjects had stage 1 hypertension without symptomatic hypokalemia; 2 had stage 2 hypertension along with symptomatic hypokalemia.

3.2. Differences of Screening Testing and Confirmatory Testing between the Control and SPECT/CT Groups (Table 1). In the control group ($n = 9$), 8 subjects had elevated PAC and one had normal PAC; 5 had suppressed PRA and 4 had nonsuppressed PRA; 8 had positive ARR and one had negative ARR; 4 had positive confirmatory testing and 5 had absent results. In the SPECT/CT group ($n = 6$), 6 subjects had elevated PAC; one had suppressed PRA and 5 had nonsuppressed PRA; 2 had positive ARR and 4 had negative ARR; 4 had negative confirmatory testing and 2 had absent results.

3.3. Differences of Imaging Modalities between the Control and SPECT/CT Groups (Table 2). CT produced 9 (100%)

true positive results in the control group. CT produced 2 (33%) false negative and 4 (67%) true positive results in the SPECT/CT group. NP-59 planar imaging produced 2 (33%) true positive and 4 (67%) false negative results. NP-59 SPECT and SPECT/CT produced 6 (100%) true positive results, indicating 100% sensitivity.

3.4. Integrated Analysis of All Features between the 2 Groups (Figure 1). We divided all 15 patients into 4 categories based on the severity of hypertension and hypokalemia: category 1 (stage 2 hypertension and hypokalemia; $n = 8$; 6 in the control group and 2 in the SPECT/CT group); category 2 (stage 1 hypertension and hypokalemia; $n = 2$; all in the control group); category 3 (stage 1 hypertension and low-normal potassium level; $n = 2$; 1 in the control group and 1 in the SPECT/CT group); category 4 (stage 1 hypertension and normal potassium level; $n = 3$; all in the SPECT/CT group). The screening testing from typical to atypical features was ordered from the top to bottom. PA

TABLE 2: Imaging and pathological data of study subjects.

Patient	Age (y)	Gender	CT result		NP-59 result			Pathological result Finding	Size (mm)	Followup improvement
			Appearance (side)	Size (mm)	Planar	SPECT	SPECT/CT			
Control group (<i>n</i> = 9)										
1	50	F	Nodule (L)	20	—	—	—	Adenoma	21	PAC, PRA, K
2	34	F	Nodule (L)	18	—	—	—	Adenoma	16	PAC, PRA, K, BP
3	58	F	Nodule (R)	17	—	—	—	Adenoma	17	PAC, PRA, K
4	32	F	Nodule (L)	20	—	—	—	Adenoma	20	PAC, K, BP
5	71	F	Nodule (L)	17	—	—	—	Adenoma	25	PAC, PRA, K, BP
6	59	M	Nodule (L)	11	—	—	—	Adenoma	10	PAC, BP
7	60	F	Nodule (R)	21	—	—	—	Adenoma	20	PAC, K
8	72	M	Nodule (R)	22	—	—	—	Adenoma	20	PAC, PRA, K, BP
9	56	F	Nodule (L)	17	—	—	—	Adenoma	17	PAC, K, BP
SPECT/CT group (<i>n</i> = 6)										
10	55	F	Normal	—	N	R	R	Micronodule	0.8	PAC, K, BP
11	48	F	Nodule (L)	17	L	L	L	Adenoma	17	PAC, PRA, K, BP
12 [†]	57	M	Enlarge (L)	9 (in thickness)	N	L	L	Focal nodular hyperplasia	6	PAC, PRA, K, BP
13	56	M	Nodule (L)	12	N	L	L	Adenoma	10	PAC, BP
14	39	M	Nodule (R)	14	N	R	R	Adenoma	12	PAC, K, BP
15 [‡]	27	F	Normal	—	Faint	Bil	Bil	— [#]	— [#]	PAC, BP

Abbreviations: CT: computed tomography; L: left; R: right; Bil: bilateral; other abbreviations are the same as Table 1.

[†]Patients 12 and 15 had stages 3 and 4 chronic kidney disease with serum creatinine level of 2.2 and 2.5 mg/dL, respectively.

[#]Patient 15 did not undergo adrenalectomy because of bilateral adrenal hyperplasia.

was easily diagnosed from the typical clinical presentations of stage 1 or 2 hypertension along with hypokalemia and typical screening testing followed by positive CT results (patients 1–3, 5, and 8). Despite the presence of atypical screening testing, PA also could be diagnosed from typical clinical presentations together with positive CT results (patients 4, 7, and 9). However, we found that the SPECT/CT group had a higher percentage of mild clinical presentations, such as stage 1 hypertension and low-normal or normal serum potassium level (patients 10, 11, 13, and 15), atypical laboratory features of PA (patients 10, 12–15), and negative CT results (patients 10 and 15). All patients were found to have an improvement of BP after adrenalectomy and/or medical treatment, except for patients 1, 3, and 7 in the control group. This table implies that the timing of using NP-59 SPECT/CT tends to categories 3 and 4, as well as atypical screening and confirmatory testing.

3.5. Relationship of NP-59 SPECT/CT Lateralization Results to Clinical Outcome and to Pathological Features (Table 2 and Figure 1). NP-59 SPECT/CT correctly identified 3 adenomas (median size, 12 mm; range 10–17 mm), 1 micronodule (0.8 mm in size), 1 focal nodular hyperplasia (with the largest micronodule 6 mm in size), and 1 bilateral adrenal

hyperplasia (Figure 2) in 6 patients. Of these 3 adenomas, 2 were not detected on planar images. 2 (33%) of the SPECT/CT group had stages 3 and 4 CKD, both of which had atypical laboratory testing. All 6 patients had a clinical improvement of BP and normalization of PAC, 4 of whom had stage 1 hypertension and cured BP.

3.6. Comparison of Parameters between the Control and SPECT/CT Groups (Table 3). The median level of serum potassium was significantly higher in the SPECT/CT group than in the control group (3.6 versus 2.6 mEq/L, resp., $P = .029$), and the median level of ARR was significantly lower in the SPECT/CT group than in the control group (18.7 versus 352.3, resp., $P = .025$). The median size of the affected adrenal gland on CT scan and pathological examination was significantly less in the SPECT/CT group than in the control group (10.5 versus 18 mm, resp., $P = .007$; 10 versus 20 mm, resp., $P = .015$). Compared with the control group, the SPECT/CT group featured lower systolic BP (147 mm Hg) and nonsuppressed PRA (1.47 ng/mL/h) although the difference was not statistically significant. Furthermore, both groups had elevated PAC (32.1 versus 28.4 ng/dL in the control and SPECT/CT group, resp.) although the difference was not statistically significant.

TABLE 3: Comparison of variables between the control and SPECT/CT groups.

Variable	Control group (<i>n</i> = 9)	SPECT/CT group (<i>n</i> = 6)	<i>P</i> [‡]
Age (y) [†]	58 (32–72)	51 (27–57)	.157
Male gender (<i>n</i> [%])	2 (22%)	3 (50%)	.329
Systolic BP (mm Hg) [†]	180 (146–230)	147 (144–206)	.077
Diastolic BP (mm Hg) [†]	105 (71–130)	90 (80–115)	.237
Serum potassium (mEq/L) [†]	2.6 (1.6–3.49)	3.6 (2.2–4.32)	.029
PAC (ng/dL) [†]	32.1 (21.7–110.7)	28.4 (25.3–37.2)	.239
PRA (ng/mL/h) [†]	0.06 (0.05–0.53)	1.47 (0.06–2.52)	.058
Aldosterone-renin ratio (ARR) [†]	352.3 (23–642)	18.7 (13–447)	.025
CT size (mm) [†]	18 (11–22)	10.5 [#] (9–17 [#])	.007
Pathological size (mm) [†]	20 (10–25)	10* (0.8–17*)	.015

Abbreviations are the same as Tables 1 and 2.

[†]Data are expressed as median (range).

[#]*n* = 4; patients 10 and 15 were excluded in this variable because of normal appearance of adrenal glands on the CT scan.

**n* = 5; patient 15 was excluded in this variable because of bilateral adrenal hyperplasia.

[‡]*P* < .05 as significant.

4. Discussion

This is the first study to report the use of NP-59 SPECT/CT in patients with normal renal function and those with CKD who are clinically suspected to have PA but have subtle clinical symptoms, atypical results on screening tests, negative confirmatory tests, or negative CT findings. This study adds novel data to existing knowledge of PA by qualitatively analyzing the associations between clinical symptoms and screening tests (Figure 1), as well as quantitatively comparing clinical and pathological parameters between control and SPECT/CT groups (Table 3). First, our findings show that the screening testing and confirmatory testing may be unreliable in subclinical PA characterized by stage 1 hypertension without symptomatic hypokalemia, and in the setting of CKD, and second, They show that NP-59 SPECT/CT imaging adds value in the diagnosis of probable PA when elevated PAC and stage 1 or 2 hypertension coexists, but the other criteria were not present.

The first part of this study qualitatively analyzed the application of NP-59 SPECT/CT in patients suspected of having PA, but clinically not confirmed, as shown in Figure 1. Only 5 patients (patients 1–3, 5, and 8) presented with typical clinical pictures, which lead to a rapid diagnosis. Most of the patients presented with atypical signs and symptoms: subclinical (stage 1 hypertension in the absence of symptomatic hypokalemia) PA (*n* = 5), nonsuppressed PRA (*n* = 9), negative ARR (*n* = 5), negative confirmatory tests (*n* = 4), and negative CT results (*n* = 2). This finding is consistent with the viewpoint of Mosso et al. [19] that PA should be considered a continuous pathological disorder, in which most of the patients present with normokalemia and a mild form, and only a minority of patients present with a classical clinical picture of PA. Furthermore, it has been reported that the saline loading testing has low accuracy in patients with normokalemic PA [9]. The lower right area of Figure 1 corresponds to difficulty in arriving at a diagnosis of PA because of subtle symptoms, atypical screening testing, inclusive confirmatory testing, or negative

CT findings and is where NP-59 SPECT/CT is useful because it allows accurate localization of tumors because of its high sensitivity and diagnostic accuracy [16]. Therefore, the diagnosis of subclinical PA cannot rely on screening testing and confirmatory testing.

In addition, it is worth noting that 2 patients with CKD (patients 12 and 15) were diagnosed with PA by means of NP-59 SPECT/CT in this study. The diagnosis of PA in patients with CKD is difficult and easily missed, and only 2 cases have been reported in the English literature [20, 21]. This is because CKD masks the typical hallmarks of PA (hypertension, hypokalemia, and low PRA), shares some features with PA (such as hypertension and elevated PAC) [22], and disturbs the renin-angiotension-aldosterone system leading to a further decrease of the response of renin/aldosterone to stimuli or suppressive manoeuvres [23]. Furthermore, PRA varies from low to high level [22], the ARR is not reliable, and there are no clear-cut levels of PAC, PRA, and ARR for the diagnosis of PA in patients with CKD [4]. Adrenal vein sampling is more risky in patients with CKD than in those with normal renal function. In this setting, NP-59 SPECT/CT allows safe lateralization and prompt decision-making.

The second part of our study analyzed the differences in clinical and pathological parameters between the 2 groups, as shown in Table 3. We found that patients using NP-59 SPECT/CT imaging tended to feature stage 1 hypertension (median BP, 147 mm Hg) and nonsuppressed PRA (median level, 1.47 ng/mL/h) and significantly had negative ARR, nearly normal serum potassium level, and smaller adrenal size on CT imaging and pathological examination. Taking together, patients with probable PA who required NP-59 SPECT/CT imaging featured subclinical or atypical presentations. We also found that PAC was elevated, but not statistically significant, in both groups, and that the control group had higher PAC and systolic BP (median level, 32.4 ng/dL; median BP, 180 mm Hg, resp.) than the SPECT/CT group (median level, 28.4 ng/dL; median BP, 147 mm Hg, resp.). These findings implied that this clinical

clue of stage 1 hypertension along with elevated PAC may be useful when initially assessing the potential for subclinical PA and that elevated PAC precedes evident hypertension in patients with subclinical PA. It has been reported that the existence of normotensive PA was featured as elevated PAC [3]. Since PA is a continuous pathological disorder [19] and prolonged hyperaldosteronism causes subsequent hypertension [5] and excessive cardiovascular damage [6], non-invasive NP-59 SPECT/CT can provide value for early diagnosis and intervention of subclinical PA and may be a reliable method to distinguish between patients with low-renin essential hypertension and subclinical PA.

The Framingham offspring study has shown that an excess of circulating aldosterone in normotensive individuals results in the development of sustained hypertension [5] and cardiovascular morbidity and mortality that is beyond the effect of hypertension alone [6]. The cost effectiveness of a workup for subclinical PA remains to be determined. However, a timely identification of subclinical PA is rewarding for a number of reasons because a long-term cure implies saving the costs of lifetime antihypertensive medications, testing for monitoring the target organ damage, and treatment of complications [24]. Furthermore, long-term cure rate of hypertension correlates with the duration and severity of hypertension and ranges from 30 to 60% [7]. In the present study, 4 patients in the SPECT/CT group presented with stage 1 hypertension and had cured hypertension, and 2 patients with stage 2 hypertension merely improved BP. Therefore, vascular remodelling and duration of hypertension emphasize the importance of an early diagnosis of subclinical or atypical features of PA for a more favorable outcome.

The present study has some limitations. First, this was a retrospective study, and confirmatory testing and NP-59 SPECT/CT were not performed in all patients. Second, the specificity and diagnostic accuracy of NP-59 SPECT/CT cannot be established because of the small number of cases. Third, all patients did not undergo adrenal vein sampling.

5. Conclusion

In summary, our findings demonstrated that NP-59 SPECT/CT could be a reliable and non-invasive tool for an early diagnosis of PA in patients with subclinical or atypical features of PA and in CKD patients with suspected PA. NP-59 SPECT/CT imaging may transform the diagnostic process and lead to early identification and prompt management of these patients to achieve the cure of hypertension.

6. Conflict of Interests

The authors have no conflict of interests.

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