ENDOCRINE FEEDBACK LOOP
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Table 1. Patient characteristics

Characteristic	All (n = 223)	No PA (n = 61)	PA (n = 162)	Comparison between groups (*P* value)
Age (years): median (Q1, Q3)	52 (43, 59)	47 (38, 58)	54 (44, 59)	0.005
Sex: n (%)				
Males	100 (44.8)	21 (34.4)	79 (48.8)	0.055
Females	123 (55.2)	40 (65.6)	83 (51.2)	
SBP (mmHg): mean (SD)	143 (19)	139 (19)	148 (18)	0.003
DBP (mmHg): mean (SD)	91 (12)	87 (11)	92 (12)	0.005
SBP > 150 and/or DBP > 100, n (%)	88 (39.5)	17 (27.9)	71 (43.8)	0.042
Resistant hypertension,[a] n (%)	42 (18.8)	7 (11.5)	35 (21.6)	
PAC				
Intra-individual average[b] (pmol/L): median (Q1, Q3)	425 (329, 577)	344 (250, 466)	451 (351, 584)	<0.001
Number of tests: mean (SD)	3.0 (1.1)	2.8 (1.1)	3.1 (1.1)	0.047
DRC				
Intra-individual average[b] (mU/L): median (Q1, Q3)	4.1 (2.5, 8.3)	13.3 (4.2, 21.5)	3.8 (2.3, 6.1)	<0.001
Number of tests: mean (SD)	3.0 (1.1)	2.8 (1.1)	3.1 (1.1)	0.043
Intra-individual average DRC < 8 mU/L, n (%)[c]	162 (72.7)	25 (41.0)	137 (84.6)	<0.001
ARR				
Intra-individual average[b] (pmol/L:mU/L): median (Q1, Q3)	107 (59, 215)	37 (21, 73)	133 (83, 237)	<0.001
With at least 1 ARR < 70: n (%)	116 (52.0)	54 (88.5)	62 (38.3)	<0.001
With first ARR < 70: n (%)	29 (13.0)	25 (41.0)	4 (2.5)	<0.001
Potassium				
Intra-individual average[b] (mmol/L): mean (SD)	4.1 (0.4)	4.2 (0.3)	4.0 (0.4)	0.002
Range of intra-individual averages (mmol/L)	2.8-4.9	2.8-4.9	3.0-4.7	
eGFR				
Intra-individual average[b] (mL/min): median (Q1, Q3)	90 (83, 90)	90 (80, 90)	90 (84, 90)	0.812
Blood test timing (AM): median (Q1, Q3)	9:31 (9:03, 10:11)	9:27 (9:00, 10:08)	9:33 (9:06, 10:11)	0.412
Interval between first and last measurement (days): median (Q1, Q3)	138 (58, 271)	91 (40, 163)	162 (80, 328)	<0.001

Abbreviations: ARR, aldosterone-to-renin ratio; DBP, diastolic blood pressure; DRC, direct renin concentration; PA, primary aldosteronism; Q1, first quartile or 25th percentile; Q3, third quartile or 75th percentile; SBP, systolic blood pressure.
[a]Resistant hypertension defined as SBP > 140 and/or DBP > 90 mmHg on 3 or more antihypertensive agents, or any BP on 4 or more antihypertensive agents.
[b]For each patient, intra-individual averages were calculated by adding all available measurements for that patient and dividing the sum by the total number of measurements available for that patient.
[c]For the 25 patients with an intraindividual average DRC > 8 mU/L, the median DRC was 8.4 (interquartile range 9.1-12). Suspicion of PA was raised by a low renin and elevated ARR, and the diagnosis of PA was confirmed by inadequate aldosterone suppression following saline infusion. For this group, the pre-saline median DRC was 11.9 mU/L and post-saline median DRC was 4.4 mU/L.

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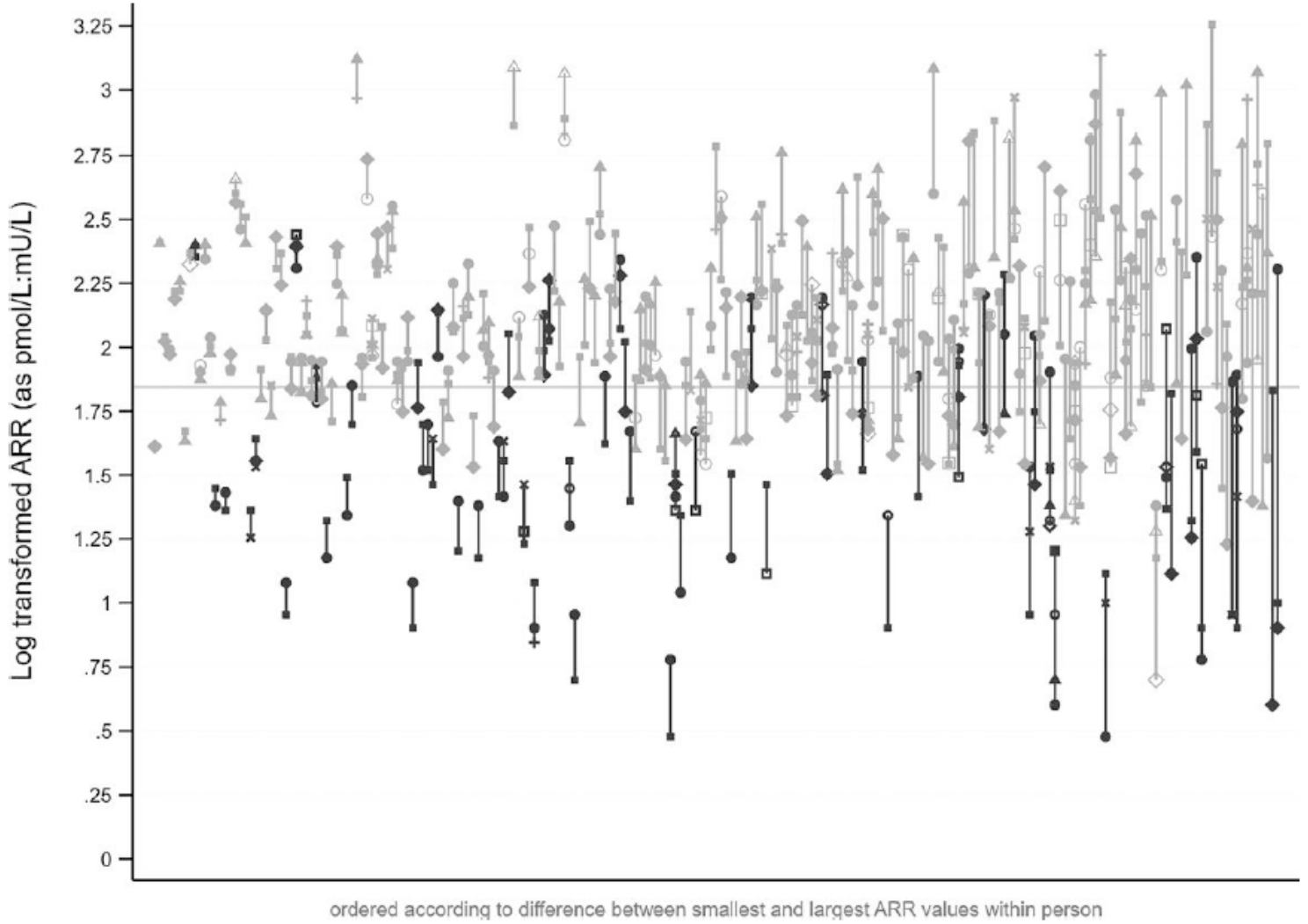

Figure 1. Log-transformed aldosterone-to-renin ratio (pmol/L:mU/L) for each individual patient, arranged from smallest to largest from left to right. The vertical gray lines represent individuals with primary aldosteronism and vertical black lines represent individuals without primary aldosteronism. The horizontal gray line represents the log-transformed aldosterone-to-renin ratio cut-off 70 pmol/L:mU/L. The shapes represent the order of measurement, in ascending order from the first measurement: filled circle, filled square, filled triangle, filled diamond, cross, "x," unfilled circle, unfilled square, unfilled triangle, unfilled diamond.

Table 2. Assessment of PAC, DRC, and ARR variability using the CV[a]

Characteristic	Sample CV_{PAC} (%)		Sample CV_{DRC} (%)		Sample CV_{ARR} (%)	
	Median (Q1, Q3)	Comparison between groups (*P*-value)	Median (Q1, Q3)	Comparison between groups (*P*-value)	Median (Q1, Q3)	Comparison between groups (*P* value)
All patients	24 (16, 35)		41 (25, 63)		42 (25, 64)	
By PA status						
–PA (n = 61)	22 (13, 37)	0.208	41 (23, 69)	0.937	42 (28, 65)	0.872
+PA (n = 162)	25 (17, 35)		42 (26, 62)		42 (24, 63)	
By PA subtype						
Unilateral (n = 41)	24 (18, 39)	0.012	51 (34, 74)	0.180	46 (25, 69)	0.640
Bilateral (n = 64)	27 (19, 36)		39 (27, 51)		41 (21, 58)	
Indeterminate (n = 40)	22 (12, 22)		39 (28, 64)		46 (27, 75)	
By sex						
Males (n = 100)	23 (16, 34)	0.215	44 (27, 67)	0.224	44 (24, 65)	0.623
Females (n = 123)	25 (18, 36)		38 (25, 60)		42 (27, 65)	
By age (years)[b]						
≤40 (n = 46)	26 (17, 41)	0.358	45 (24, 69)	0.506	42 (28, 63)	0.524
41-60 (n = 126)	22 (16, 35)		42 (25, 63)		46 (26, 67)	
>60 (n = 49)	23 (18, 30)		39 (27, 60)		41 (25, 63)	
By hypokalaemia status ($K^+ < 3.5$ at any point)						
–Hypokalaemia (n = 195)	23 (16, 35)	0.025	40 (25, 60)	0.036	41 (25, 62)	0.238
+Hypokalaemia (n = 28)	28 (14, 40)		55 (28, 78)		49 (27, 72)	
By first eGFR measure						
≥ 60 (n = 214)	24 (16, 35)	0.642	41 (26, 63)	0.614	43 (25, 64)	0.427
<60 (n = 9)	35 (16, 74)		33 (22, 48)		33 (27, 55)	
By blood pressure						
Others (n = 132)	24 (17, 35)	0.221	39 (25, 61)	0.214	41 (25, 62)	0.569
SBP > 150 and/or DBP > 100 (n = 88)	22 (14, 38)		44 (24, 68)		44 (26, 71)	

Abbreviations: ARR, aldosterone-to-renin ratio; CV, coefficient of variation; DBP, diastolic blood pressure; DRC, direct renin concentration; eGFR, estimated glomerular filtration rate; PA, primary aldosteronism; PAC, plasma aldosterone concentration; Q1, first quartile or 25th percentile; Q3, third quartile or 75th percentile; SBP, systolic blood pressure.
[a]Sample CV is calculated from $\log_{10}$ transformed data due to the large heteroskedasticity (ie, increase in SD as the mean increased) and the CV formula (16).
[b]No significant interaction between males and females; therefore variability is comparable.

Table 3. Assessment of PAC, DRC, and ARR variability using the PD

Characteristic	PD_{PAC} (%)		PD_{DRC} (%)		PD_{ARR} (%)	
	Median (Q1, Q3)	Comparison between groups (*P*-value)	Median (Q1, Q3)	Comparison between groups (*P*-value)	Median (Q1, Q3)	Comparison between groups (*P* value)
All patients	45 (28, 61)		75 (40, 111)		71 (41, 115)	
By PA status						
–PA (n = 61)	38 (22, 61)	0.011	65 (34, 129)	0.400	61 (41, 108)	0.106
+PA (n = 162)	46 (31, 61)		76 (49, 107)		74 (41, 121)	
By PA subtype						
Unilateral (n = 41)	44 (31, 67)	0.227	93 (50, 117)	0.055	80 (46, 128)	0.769
Bilateral (n = 64)	49 (39, 69)		69 (50, 102)		72 (39, 115)	
Indeterminate (n = 40)	38 (22, 52)		82 (47, 106)		84 (40, 109)	
By sex						
Males (n = 100)	42 (25, 60)	0.218	69 (40, 116)	0.337	67 (38, 109)	0.523
Females (n = 123)	47 (30, 64)		77 (43, 107)		73 (47, 120)	
By age (years)[a]						
≤40 (n = 46)	53 (24, 77)	0.011	79 (47, 128)	0.870	65 (42, 121)	0.502
41-60 (n = 126)	44 (28, 60)		75 (38, 116)		75 (41, 122)	
>60 (n = 49)	41 (28, 55)		72 (43, 96)		71 (37, 102)	
By hypokalaemia status ($K^+ < 3.5$ at any point)						
–Hypokalaemia (n = 195)	44 (28, 60)	0.576	70 (40, 108)	0.015	69 (41, 108)	0.372
+Hypokalaemia (n = 28)	48 (28, 77)		94 (41, 142)		87 (49, 130)	
By first eGFR measure						
≥ 60 (n = 214)	45 (28, 60)	0.468	75 (42, 111)	0.329	72 (41, 115)	0.565
<60 (n = 9)	70 (26, 111)		61 (32, 66)		57 (45, 109)	
By blood pressure						
Others (n = 132)	49 (31, 62)	0.001	75 (41, 113)	0.562	68 (44, 114)	0.580
SBP > 150 and/or DBP > 100 (n = 88)	38 (23, 57)		69 (41, 113)		73 (38, 119)	

Abbreviations: ARR, aldosterone-to-renin ratio; DBP, diastolic blood pressure; DRC, direct renin concentration; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; PA, primary aldosteronism; PD, percent difference; Q1, first quartile or 25th percentile; Q3, third quartile or 75th percentile; SBP, systolic blood pressure.

[a]No significant interaction between males and females; therefore variability is comparable.

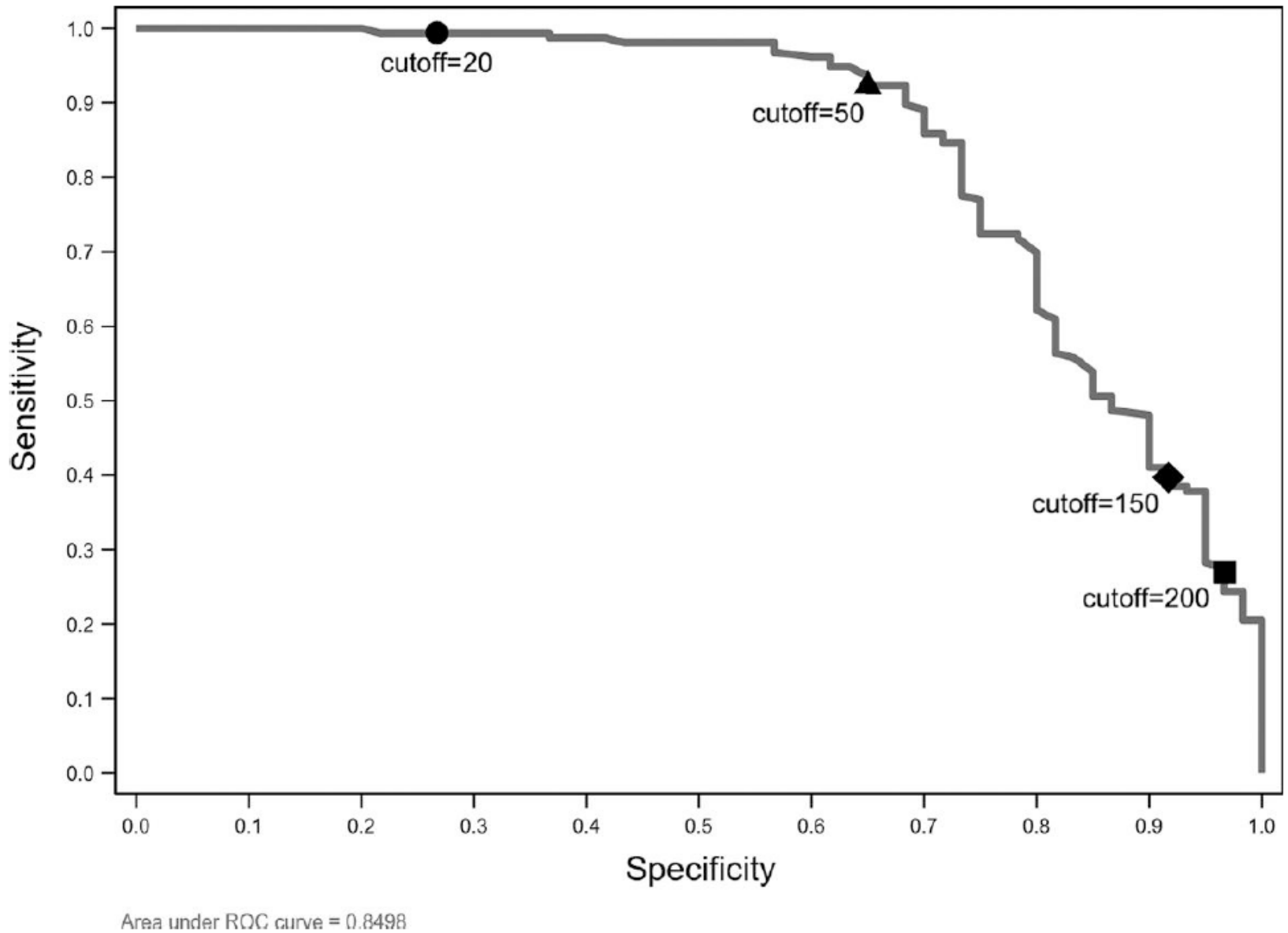

Figure 2. Plot of sensitivity against specificity of ARR cut-offs for diagnosing PA. The circle represents an ARR of 20 pmol/L:mU/L, the triangle ARR 50 pmol/L:mU/L, the diamond ARR 150 pmol/L:mU/L, and the square ARR 200 pmol/L:mU/L. The area under the receiver operating curve is 0.8498. ARR, aldosterone-to-renin ratio; PA, primary aldosteronism.

Table 4. Predictive value of initial ARR based on different cut-off values

ARR cut-off	Sensitivity Est (95% CI)	Specificity Est (95% CI)	PPV Est (95% CI)	NPV Est (95% CI)	AUC (Est)
>70 pmol/L:mU/L (2.5 ng/dL:mU/L)	84% (77-89)	73% (60-84)	89% (83-94)	64% (51-75)	0.787
>150 pmol/L:mU/L (5.4 ng/dL:mU/L)	39% (31-47)	92% (82-97)	92% (83-98)	37% (29-45)	0.654
>200 pmol/L:mU/L (7.2 ng/dL:mU/L)	26% (20-34)	97% (89-100)	95% (84-99)	34% (27-41)	0.615

ARR as pmol/L:mU/L presented rounded to the nearest whole number as a multiple of 5. Conversion of plasma aldosterone concentration from pmol/L to ng/dL utilized a conversion factor of 27.74.
Abbreviations: ARR, aldosterone:renin ratio; AUC, areas under the curve; Est, estimate; NPV, negative predictive value; PPV, positive predictive value.