Computed tomography combined with confirmatory tests for the diagnosis of aldosterone-producing adenoma

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Abstract. Primary aldosteronism (PA) is the most common cause of secondary hypertension, and a simpler non-invasive method for identification of aldosterone-producing adenoma (APA) is required to improve the standard of medical treatment for PA patients. We retrospectively analyzed the clinical data of hypertensive patients with an aldosterone/renin ratio (ARR) ≥30 (ng/dL)/(ng/mL/h), and surgical and/or adrenal venous sampling (AVS) results served as the gold standard for APA diagnosis. The study aimed to determine whether positive CCT and SIT results plus a unilateral adrenal nodule found by CT allow unambiguous identification of an APA with high diagnostic specificity. Clinical data from 71 APA and 47 non-APA patients were collected, and logistic regression analysis was performed to construct models. Receiver operating characteristic (ROC) curves were used to analyze the efficacy of diagnostic tests. The areas under the ROC curves (AUCs) were similar between the post-SIT plasma aldosterone concentration (PAC) and post-CCT PAC (p > 0.05). The optimal post-SIT and post-CCT PAC cutoff values were 17.2 and 21.2 ng/dL, respectively. Positive CT findings combined with a post-SIT PAC >17.2 ng/dL or post-CCT PAC >21.2 ng/dL provided specificities of 97.8% and 95.7% for predicting APA, respectively. Logistic diagnostic models 1 (M1, CT finding + post-SIT PAC) and 2 (M2, CT finding + post-CCT PAC) were built, which showed equivalent diagnostic value (AUC = 0.959 and 0.932, respectively) (p > 0.05). The models combining CT findings with post-SIT PACs or post-CCT PACs represent an easier method to distinguish APA patients from other hypertensive patients with positive upright ARR results, especially in primary care where AVS may be unavailable.

Key words: Aldosterone-producing adenoma, Adrenal computed tomography, Captopril challenge test, Sodium infusion test

PRIMARY ALDOSTERONISM (PA) is the most common cause of secondary hypertension. The prevalence of PA ranges from 3.9% in hypertensive stage I to 11.8% in hypertensive stage III [1], and the prevalence is approximately 7.1% among patients with resistant hypertension [2]. The most common subtypes of PA are aldosterone-producing adenoma (APA) and idiopathic aldosteronism (IHA). As APA is surgically curable, more than 94% of patients achieve biochemical remission after surgical removal of APA [3]; thus, subtype testing is a key step in the diagnosis of and the choice of treatment for PA.

Although AVS is recommended as an essential step for subtype classification, AVS requires multiple-vein drainage, selective cannulation of contributory veins not draining an aldosterone-producing adenoma, or asymmetrical cortisol secretion [4, 5]. In addition, several other AVS procedure-related factors, such as the use of cosyntropin, sequential or simultaneous sampling of adrenal veins, or varying criteria for selectivity and lateralization, can affect AVS interpretation [6-8]. More importantly, only a limited number of specialized centers can carry out the test, with the costs of the procedure preventing its wider application as a standard diagnostic procedure. A simpler non-invasive method for subtype classification is therefore required to improve the standard of medical treatment for patients with PA.

Existing guidelines recommend a computed tomography (CT) scan of the adrenal glands as the initial examination...
to identify the subtypes of PA [9]. However, CT scans cannot depict whether adrenal adenomas on the image have the function of autonomous secretion of aldosterone. We previously reported that the degree of abnormalities in confirmatory tests, such as the captopril challenge test (CCT) and saline infusion test (SIT), predicted the PA subtype [10, 11]. However, these tests cannot be used as a substitute for AVS because of insufficient diagnostic accuracy and the extent of overlap between the two subtypes.

In this study, we retrospectively analyzed the clinical data, adrenal CT reports and CCT and SIT results of hypertensive patients with an aldosterone/renin ratio (ARR) ≥30 (ng/dL)/(ng/mL/h). We used surgery and/or AVS results as the gold standard to determine whether unilateral adrenal lesions found by CT plus positive CCT and SIT results allow unambiguous identification of an APA with high diagnostic specificity. The aim of this study was to identify an accurate, economical and practical method for diagnosing APA.

**Participants and Methods**

**Participants**

We retrospectively screened the clinical data of hypertensive patients who were referred to the West China Hospital between June 2012 and November 2017 for suspected PA and met the inclusion and exclusion criteria described below.

Inclusion criteria: 1) an upright ARR ≥30 (ng/dL)/(ng/mL/h); 2) available CCT and SIT results; 3) available enhanced thin-slice adrenal CT reports; 4) normal plasma catecholamine, urine free cortisol, and serum creatinine levels and urinalysis results; and 5) no stenosis of the bilateral renal arteries as confirmed by Doppler ultrasound.

Exclusion criteria: 1) recumbent plasma renin active (PRA) ≥12 ng/mL/h (the maximum level that our laboratory can measure); 2) familial hyperaldosteronism and aldosterone-producing adrenocortical carcinoma; 3) CT showing a unilateral or bilateral adrenal nodule but no AVS results or adrenalectomy with pathological findings; 4) a history of severe liver disease or liver enzymes greater than 2-times the upper limit of normal; and 5) cardiac insufficiency (The New York Heart Association (NYHA) grade ≥3).

**Data collection**

We collected eligible subjects from the Biomedical Big Data Research Center of West China Hospital of Sichuan University. Informed consent was obtained from the participants of the study. The subjects’ clinical and personal data were recorded, including age, sex, telephone number, body mass index (BMI), blood pressure control and hypertensive medications before admission and during hospitalization, complete blood counts and urinalysis results, blood biochemistry results (including serum electrolyte levels and liver and kidney function tests), the recumbent plasma aldosterone concentration (PAC), the upright ARR, CCT and SIT results, plasmatic and urinary catecholamines, plasmatic cortisol, 24-hour urinary-free cortisol levels, AVS and adrenal CT scan results, and (for patients who underwent adrenalectomy) operative surgical recordings and postoperative pathological findings. We followed up by phone to record the blood pressure, hypertensive agents, serum potassium levels and ARRs of the patients who had undergone adrenalectomy or taken mineralocorticoid receptor antagonists (MRAs).

**APA diagnostic criteria**

We set the APA diagnostic criteria based on previous studies [11-13]. An aldosterone-producing adenoma (APA) was diagnosed based on the following criteria: (1) a surgically and pathologically confirmed unilateral adrenal adenoma with a normal ARR postoperatively; (2) an outcome of adrenalectomy at the follow-up characterized by normokalemia and cured or improved hypertension 3 months after adrenalectomy [3]; (3) lateralization of aldosterone secretion on AVS.

**Measurement of the ARR and the SIT and CCT procedures**

Before the tests, MRAs and potassium-wasting diuretics were withdrawn for at least 4 weeks. Other agents, including beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, were withdrawn for at least 2 weeks. Patients with hypokalemia received oral supplementation of potassium to maintain plasma potassium within the normal range.

Measurement of the upright ARR: Blood samples for upright PAC and PRA measurements were collected after the patient remained in a sitting or standing position for at least 2 h and was seated for 15 min. The ARR was calculated as PAC (ng/dL)/PRA (ng/mL/h). Both PRA and the PAC were measured by radioimmunoassay. The commercial PRA kit was provided by Atomic Hi-Tech Co., Ltd., China. The intra- and inter-assay coefficients of variation for PRA were less than 10% and less than 15%, respectively. The commercial PAC kit was provided by Jiuding Medical Biological Engineering Co., Ltd., China. The intra- and inter-assay coefficients of variation for PAC were 7.3% and 9.6%, respectively. The normal reference ranges of the PAC kit are 4.5–17.5 ng/dL (supine) and 9.8–27.5 ng/dL (upright). The maximum and minimum levels that the PAC kit can measure are 200 and 0.37 ng/dL, respectively.
CCT: Blood samples were drawn for measurement of PRA and the PAC at baseline after the patient remained in a sitting or standing position for at least 2 h. Then, patients received 25 mg of captopril orally, and blood samples were drawn again to measure PRA and the PAC at 2 h after taking captopril, with the patient remaining seated during this period.

SIT: Blood samples for recumbent PAC and PRA measurements were drawn in the morning when patients were still in bed. Patients remained in the recumbent position during a continuous infusion of 2 L of 0.9% saline iv over 4 h, and blood samples for post-SIT PAC and PRA measurements were drawn at the end of infusion.

Adrenal venous sampling
AVS without ACTH stimulation was performed in the morning. A catheter was guided from the right femoral vein into the adrenal vein and infra renal inferior vena cava (IVC). Blood samples were simultaneously obtained from IVC and bilateral adrenal veins. Adrenal venous cannulation was considered successful when the selectivity index (SI) was ≥2.0. Lateralization of aldosterone secretion is determined by the lateralization index (LI), and unilateral aldosterone hypersecretion was diagnosed when the LI was ≥2.0 based on guidelines [14].

Statistical analysis
Statistical analysis was performed with SPSS 23 and MedCalc 19.05 statistical software. The patients’ clinical characteristics (if blood pressure or serum potassium was measured more than once, the mean value was recorded) were recorded, and the mean ± standard deviation (SD) and the median (25th to 75th percentiles) were used to express continuous variables with and without a normal distribution, respectively. Continuous variables that passed tests for normality and equal variance were compared between groups by Student’s t test. The rank-sum test was used for the continuous variables that did not pass these tests. The sex ratio was compared between groups using the chi-squared test. Receiver operating characteristic (ROC) curves were used to determine the diagnostic value of CCT and SIT results in diagnosing APA, and we also calculated the areas under the ROC curves (AUCs), the optimal cutoff points and the associated sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (–LR), positive predictive value (PPV) and negative predictive value (NPV). The Z test was used to determine significant differences between the AUCs. Based on logistic regression, we combined CT findings with different confirmatory tests and developed diagnostic models for APA diagnosis. P < 0.05 was considered statistically significant.

Results
Characteristics of the patients
A total of 118 patients (71 patients with APA and 47 patients with non-APA) were enrolled in this study, and all enrolled patients had data for the upright ARR, SIT, CCT, and CT results. Eighty-eight patients underwent AVS, 85 of whom underwent the procedure successfully; 61 patients showed lateralization of aldosterone secretion on AVS, and 3 patients had AVS failure with the right adrenal vein and were enrolled in the APA group according to their pathology and follow-up results. Seventy patients with APA underwent adrenalectomy, and the pathological results showed adrenal cortical adenoma. Among the 70 patients, 4 patients were lost to the follow-up, complete clinical remission was achieved in 21 patients, and partial clinical success was observed in 42 patients. Sixty-six patients achieved complete biochemical remission after surgery. The cohort’s characteristics are presented in Table 1. The post-CCT PAC, post-SIT PAC and upright ARR of the APA group were higher than those of the non-APA group (p < 0.05), whereas the serum potassium level in the APA group was significantly lower than that in the non-APA group (p < 0.001). No significant between-group differences in other characteristics were identified (p > 0.05).

Diagnostic value and optimal cutoff point of CCT for PA diagnosis
ROC curves were used to analyze the post-CCT efficacy of the ARR, PAC, PRA and PAC suppression percentage for APA diagnosis (Fig. 1). The AUC of the post-CCT PAC was 0.818 (95% CI 0.737–0.883), which was significantly higher than those of the post-CCT ARR, PAC and PRA suppression rate (p < 0.05) (Table 2). The optimal cutoff value of the post-CCT PAC was 21.2 ng/dL, with a sensitivity of 88.7% and a specificity of 78.7%.

Optimal cutoff point of SIT for APA diagnosis
As shown in Fig. 2 and Table 2, the AUC of the post-SIT PAC for APA diagnosis was 0.877 (95% CI 0.804–0.930). The difference between the AUCs of the post-SIT and post-CCT PACs was not statistically significant (Z = 1.59 p = 0.111). The optimal cutoff value of the post-SIT PAC was 17.2 ng/dL, with a sensitivity of 88.7% and a specificity of 78.7%.

Diagnostic value of thin-slice adrenal CT for PA diagnosis
A positive CT finding was defined by a unilateral adrenal nodule with a normal contralateral gland. Sixty-seven of 79 patients with a positive CT finding were
diagnosed with APA by AVS and/or postoperative pathology, while four patients with APA had a negative CT finding.

The diagnostic value of CT findings combined with the post-SIT PAC or post-CCT PAC

In this study, we used a post-SIT PAC level of 17.2 ng/dL as the cutoff value. As shown in Table 3, 62 patients had positive CT and post-SIT PAC results. Among the 62 patients, 61 patients were diagnosed with APA by AVS and/or postoperative pathology, and the specificity and PPV were 97.8% (46/47) and 98.4% (61/62), respectively.

We used a post-CCT PAC level of 21.2 ng/dL as the cutoff value. Fifty-four of 56 patients had positive CT and post-CCT PAC results indicative of APA, with a specificity of 95.7% (45/47) and a PPV of 96.4% (54/56).

We combined CT findings with the post-SIT PAC and built diagnostic model 1 (M1). Binary logistic regression analysis showed that both CT findings (OR = 54.6, 95% CI 10.8–275, p < 0.001) and the post-SIT PAC (OR = 1.25, 95% CI 1.13–1.40, p < 0.001) were significant independent predictors of APA. The logistic function was as follows: Prediction score 1 (pre-1) = e^X/(1 + e^X), where X = –6.8 + 0.226* post-SIT PAC + 4* CT finding (positive CT finding = 1, negative CT finding = 0).

Then, CT findings were combined with the post-CCT PAC. CT findings (OR = 38.9, 95% CI 10.4–146, p < 0.001) and post-CCT PAC (OR = 1.1, 95% CI 1.03–1.18, p < 0.001) independently predicted APA and were used in diagnostic model 2 (M2): Prediction score 2 (pre-2) = e^X/(1 + e^X), where X = –4.38 + 0.097*post-CCT PAC + 3.66*CT finding (positive CT finding = 1, negative CT finding = 0). We drew ROC curves for M1 and M2 based on pre-1 and pre-2, respectively, and calculated the

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**Table 1** Characteristics of the cohort

| Variables                  | APA          | Non-APA       | p value |
|----------------------------|--------------|---------------|---------|
| Number                     | 71           | 47            | —       |
| Age (y)                    | 45.9 ± 11.9  | 49.9 ± 10.6   | 0.060   |
| Sex (male/female)          | 27/44        | 20/27         | 0.702   |
| BMI (kg/m²)                | 23.9 ± 3.36  | 24.4 ± 3.57   | 0.515   |
| SBP (mmHg)                 | 155 ± 22     | 147 ± 18      | 0.127   |
| DBP (mmHg)                 | 95 ± 15      | 90 ± 14       | 0.164   |
| Serum Na⁺ (mmol/L)         | 143 ± 3.99   | 143 ± 7.47    | 0.605   |
| Serum K⁺ (mmol/L)          | 3.26 ± 0.423 | 3.61 ± 0.429  | <0.001  |
| Duration of HT* (y)        | 4.8 (1.5, 8.5)| 5.0 (2.0, 9.5) | 0.555   |
| DM/prediabetes (n%)        | 30.9         | 31.9          | 0.997   |
| CVD (n%)                   | 40.8         | 29.8          | 0.246   |
| Upright ARR* (ng/dL)/(ng/mL/h) | 139 (63.1, 278) | 78.6 (41.6, 126) | 0.001   |
| Post-CCT PAC* (ng/dL)      | 28.5 (21.9, 35.7) | 18.7 (13.9, 21.2) | <0.001 |
| Post-CCT ARR* (ng/dL)/(ng/mL/h) | 133 (48.0, 350) | 92.4 (41.4, 205) | 0.209   |
| Post-SIT PAC* (ng/dL)      | 26.6 (20.8, 33.6) | 13.6 (10.7, 16.9) | <0.001 |

* median (p25, p75). BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; HT, hypertension; DM, diabetes mellitus.
AUCs for the models (Fig. 3). The AUC of M1 was 0.959 (95% CI 0.907–0.988), which was slightly higher than the AUC of M2 (AUC = 0.932, 95% CI 0.870–0.970), but the difference did not reach statistical significance (p > 0.05).

**Discussion**

The detection rate of PA has increased with the application of ARR measurements in high-risk hypertensive populations [15]. Numerous clinical studies verified that subjects with PA are more likely to develop cardiovascular and renal damage, abnormal glucose metabolism, and osteoporosis than subjects with essential hypertension (EH) [16-19], and that these risks could be effectively improved in APA subjects after adrenalectomy, resulting in better clinical and biochemical outcomes [20, 21]. On the other hand, some research findings in recent years led endocrinologists to believe that IHA is not clearly distinct from EH, such as low renin essential hypertension (LREH). In fact, some endocrinologists consider that IHA and LREH are 2 states within a disease spectrum [22, 23], and that hypertensive patients with inappropriate renin suppression or elevated circulating aldosterone concentrations should be treated with MRAs whether they have EH or IHA [24, 25]. Therefore, distinguishing APA patients from hypertensive patients with a positive screening test is crucial [ARR ≥30 (ng/dL)/(ng/mL/h)].

In this study, we used surgical and/or AVS results as the gold standard to analyze the value of adrenal CT, the CCT, and the SIT in the diagnosis of APA. Sixty-seven of 79 patients with positive CT findings were diagnosed with APA by AVS and/or postoperative pathology, and four patients with APA had negative CT findings. That is, the coincidence rate of a CT diagnosis and a final AVS/or surgical diagnosis of APA in hypertensive patients with a positive screening test was 86.4% (102/118). If CT results are used as the basis for APA diagnosis, the false-positive and false-negative rates are 25.5% and 5.63%, respectively. A retrospective study in

**Table 2** The value of SIT and CCT for APA diagnosis

|                      | AUC 95% CI | Optimal cutoff value | Sensitivity | Specificity | PPV  | NPV  | +LR  | –LR  |
|----------------------|------------|----------------------|-------------|-------------|------|------|------|------|
| Post-CCT ARR (ng/dL)/(ng/mL/h) | 0.570<sup>a</sup> 0.474–0.662 | 166 | 46.4% | 71.1% | 70.8% | 46.7% | 1.61 | 0.75 |
| Post-CCT PAC (ng/dL)   | 0.818 0.737–0.883  | 21.2 | 80.3% | 76.6% | 83.8% | 72.0% | 3.43 | 0.26 |
| Post-CCT PAC suppression % | 0.512<sup>a</sup> 0.419–0.606 | 18.9 | 14.08% | 72.34% | 43.5% | 35.8% | 0.51 | 1.19 |
| Post-CCT PRA (ng/mL/h) | 0.522<sup>a</sup> 0.426–0.616 | 0.58 | 23.19% | 88.89% | 75.9% | 43.4% | 2.09 | 0.86 |
| Post-SIT PAC (ng/dL)   | 0.877 0.804–0.930 | 17.2 | 88.7% | 78.7% | 86.3% | 82.2% | 4.17 | 0.14 |

<sup>a</sup>: p < 0.05 vs. post-SIT PAC  
<sup>b</sup>: p < 0.05 vs. post-CCT PAC

Fig. 2 ROC curve of the post-SIT PAC for APA diagnosis

**Table 3** (A) the concordance between CT finding and post-SIT PAC

| Group             | CT finding |
|-------------------|------------|
|                   | positive   | negative  |
| Positive post-SIT PAC (>17.2 ng/dL) | 62 | 12 |
| Negative post-SIT PAC (<17.2 ng/dL)  | 17 | 27 |

**Table 3** (B) the concordance between CT finding and post-CCT PAC

| Group             | CT finding |
|-------------------|------------|
|                   | positive   | negative  |
| Positive post-CCT PAC (>21.2 ng/dL) | 56 | 12 |
| Negative post-CCT PAC (<21.2 ng/dL)  | 23 | 27 |
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Japan found that the diagnostic agreement between CT and AVS in 1591 PA patients was 68.1% [26]. The study by MULATERO et al. showed that if the AVS result is used as the standard, the sensitivity of CT for PA typing is 87%, and the specificity is 71% [27]. A systematic review by KEMPERS et al. [28] confirmed that inconsistent results between CT/MRI and AVS accounted for 37.8% of patients’ data. The data from our study are basically consistent with those of the above study, indicating that diagnosing APA based only on CT results may lead to unnecessary surgery.

The SIT and CCT are confirmatory tests for PA diagnosis recommended by current guidelines [9]. We previously reported that PACs at baseline and post-SIT and post-CCT PACs in APA patients were significantly higher than those in IHA and EH patients [10, 11]. However, the cutoff values of these two tests for APA diagnosis are not clear. In the current study, the AUC of the post-SIT PAC for APA diagnosis was 0.877 (95% CI 0.804–0.930), and the optimal cutoff value of the post-SIT PAC was 17.2 ng/dL, with a sensitivity of 88.7% and a specificity of 78.7%. If the post-SIT PAC is used as the diagnostic criterion for APA, the false-positive and false-negative rates are 11.3% and 21.3%, respectively. The AUC of the post-CCT PAC was 0.818 (95% CI 0.737–0.883), which was significantly higher than those of the post-CCT ARR, PAC and PRA suppression rate. The optimal cutoff value for the post-CCT PAC was 21.2 ng/dL, with a sensitivity of 80.3% and a specificity of 76.6%. If the post-CCT PAC is used as the diagnostic criterion for APA, the false-positive and false-negative rates are 19.7% and 23.4%, respectively. The study from Hashimura et al. took a post-SIT PAC <300 pmol/L as the diagnostic standard for bilateral PA, and the sensitivity and specificity were only 76.2% (95% CI 60.5–87.9%) and 75.8% (95% CI 57.7–88.9%), respectively [29]. Another study also showed that neither the post-CCT ARR nor the PAC alone is a perfect substitute for AVS [30]. Therefore, the specificity of the CCT and SIT as diagnostic criteria for APA is not yet satisfactory based on the current research results.

Subtype diagnosis of PA has been the subject of intense scholarly debate. Considering the accuracy of adrenal CT or the CCT, the SIT alone as a diagnostic method for APA is not satisfactory, and researchers have built some other diagnostic models as substitutes for AVS. Studies found that when CT was combined with other parameters such as serum potassium or BMI, the diagnostic value for APA could be improved [13, 26]. Troy HP et al. used the baseline aldosterone-to-lowest potassium ratio (APR, ng/dL/mmol/L) to predict unilateral PA, and the results showed that the probability of unilateral PA was 91.4% with an APR greater than 15 [31]. Hashimura H et al. reported that the combination of the post-SIT PAC and the ARR could effectively predict subtypes of PA [29]. In this study, we combined CT findings with the post-SIT PAC or post-CCT PAC, and the results showed that a positive CT finding plus a post-SIT PAC >17.2 ng/dL provided 97.8% specificity in predicting APA. When both the post-CCT PAC >21.2 ng/dL and CT findings were positive, the specificity reached up to 95.7%. We also combined CT findings with SIT or CCT results and established logistic regression models. M1 and M2 showed similarly high diagnostic accuracies (based on AUCs). Conducting the SIT requires patients to be in the hospital during the test, and the SIT may increase the risk of hypertension, cardiac insufficiency, arrhythmia and so on [32]. Our data indicated that M2, which included CT findings and the post-CCT PAC, may be the best diagnostic method as outpatients can be diagnosed definitively and effectively with reduced medical costs.

Our study had some limitations. First, this was a retrospective study; therefore, the results should be interpreted cautiously. Most patients in the study were from western China, and a multicenter study with a larger sample size is required to verify the results of our study.

In conclusion, this study developed a subtype prediction model that is easy to perform and convenient for diagnosing APA and is far less expensive than AVS. For hypertensive patients with a positive ARR and unilateral adrenal nodules identified on CT, the specificity of diagnosing APA can reach 95% if the post-CCT PAC is >21.2 ng/dL or the post-SIT PAC is >17.2 ng/dL. AVS is only needed when CCT or SIT results are positive but...
adrenal CT indicates bilaterally enlarged or normal glands. Since this study is a retrospective study, the results require further confirmation by prospective clinical trials.

Disclosure

This study did not require any funding or support. The authors have no conflicts of interest.

Availability of data

Restrictions apply to the availability of the data generated or analyzed during this study to preserve participant confidentiality. The corresponding author will detail the restrictions and any conditions under which access to some data may be provided upon request.

Ethics approval

Ethical approval was waived by the local Ethics Committee of Sichuan University in view of the retrospective nature of the study and all the procedures performed being part of routine care.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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