

● *Original Contribution*

## QUANTITATIVE TRANSCRANIAL SONOGRAPHY EVALUATION OF SUBSTANTIA NIGRA HYPERECHOGENICITY IS USEFUL FOR PREDICTING LEVODOPA-INDUCED DYSKINESIA IN PARKINSON DISEASE

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**Abstract**—Levodopa-induced dyskinesia (LID) is a common motor complication in Parkinson disease (PD). Abnormal substantia nigra hyperechogenicity (SN+), detected by transcranial sonography (TCS), plays an important role in the differential diagnosis of PD. The purpose of this study was to investigate the predictive performance of quantitative SN+ evaluations for LID. Five hundred sixty-two individuals were included in our analysis, and 198 individuals were followed up. These individuals were divided into two groups at baseline: the PD with LID (PD+LID) group and the PD without LID (PD-LID) group. The association between total hyperechogenic area of the SN on both sides (SN<sub>T</sub>) and LID was analyzed by binary logistic analysis. A binary logistic regression model including SN<sub>T</sub> was applied to establish a model for discriminating LID. At baseline, 105 (18.7%) individuals were diagnosed with LID. The PD+LID group had a longer disease duration, shorter education duration, higher levodopa equivalent doses, greater disease severity and larger SN<sub>T</sub>. A model combining clinical features and SN<sub>T</sub> was further established with better efficiency (area under the receiver operating characteristic curve = 0.839). One hundred ninety-eight individuals were followed up; individuals with a larger SN<sub>T</sub> and a higher predicted probability were more likely to develop LID in our follow-up. Our study determined that quantitative TCS evaluation of SN echogenicity is useful in predicting LID in PD. (E-mail: [liuchunfeng@suda.edu.cn](mailto:liuchunfeng@suda.edu.cn)) © 2022 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Key Words:** Transcranial sonography, Substantia nigra, Hyperechogenicity, Parkinson disease, Dyskinesia.

**Abbreviations:** PD, Parkinson's disease; LID, levodopa-induced dyskinesia; TCS, transcranial sonography; SN, substantia nigra; SN+, substantia nigra hyperechogenicity; SN<sub>T</sub>, total hyperechogenic area of the SN on both sides; SN<sub>L</sub>, the larger area of SN+ of two sides; UPDRS, Unified Parkinson's Disease Rating Scale; H-Y scale, Hoehn and Yahr scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; ROC, receiver-operating characteristic; AUC, area under the curves; K-M curves, Kaplan-Meier curves.

### INTRODUCTION

Parkinson disease (PD) is one of the most common neurodegenerative movement disorders, and is characterized

by bradykinesia, resting tremor, rigidity and postural instability (Kalia and Lang 2015; Kulisevsky et al. 2018). The pathology of PD is widely considered to be the lack of levodopa, which can be caused by the degeneration of dopaminergic neurons originating in the substantia nigra pars compacta (Dauer and Przedborski 2003; Chen et al. 2020). After decades of clinical practice, levodopa has been proven to be the standard treatment for PD (Radhakrishnan and Goyal 2018; Armstrong and Okun 2020).

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With long-term use of levodopa, some individuals with PD may develop levodopa-induced dyskinesia (LID), which is accompanied by various abnormal movements, including chorea, akathisia and dystonia (Guridi et al. 2012). In addition to levodopa, dopamine receptor agonists (pramipexole, ropinirole, etc.) can also induce dyskinesia (Tran et al. 2018; Chen et al. 2020). According to previous studies, the prevalence of LID could be as high as 10%–40% (Manson et al. 2012; Tran et al. 2018; Turcano et al. 2018; Kelly et al. 2019), which may greatly affect the quality of life of individuals with PD and their families. Because of this additional problem, LID is gaining increasing attention among patients and clinicians. To date, the detailed mechanism underlying LID remains unclear; however, sex, body weight, age, age at onset, duration of disease and treatment have been shown to be associated with LID (Sharma et al. 2010; Warren Olanow et al. 2013; Eusebi et al. 2018; Iwaki et al. 2021; Luca et al. 2021). White matter hyperintensity was reported as a risk factor for LID (Chung et al. 2020). Additionally, genetic factors may also play a role in the mechanism of LID (Kim et al. 2020; Tirozzi et al. 2021). And in recent studies, wearable sensors were considered useful in estimating the severity of LID (Hssayeni et al. 2020; Knudson et al. 2020).

Transcranial sonography (TCS) is a non-invasive neuroimaging technique, and is regarded as a useful method (by detecting substantia nigra [SN] echogenicity) in providing evidence for PD diagnosis (Berg et al. 2008; Prati et al. 2017; Zhou et al. 2018) with considerable sensitivity and specificity (Li et al. 2016, 2020a, 2020b; Toomsoo et al. 2016; Xu et al. 2020). In addition, abnormal SN hyperechogenicity (SN+) and a larger hyperechogenic area of the SN were indicated to be associated with the subtype of PD and disease severity (Zhou et al. 2016; Sheng et al. 2017; Yu et al. 2018), which revealed an important clinical application of TCS in PD. To date, studies focusing on the potential associations between SN+ and motor complications in PD are lacking. On the basis of the aforementioned evidence, we assumed that LID is associated with SN+. In this study, we attempted to determine the potential associations between SN+ and LID and to establish a prediction model for LID.

## METHODS

### *Individuals and study design*

We recruited 601 individuals with PD from the Department of Neurology of the Second Affiliated Hospital of Soochow University (Suzhou, China) from April 2015 to 2021. All participants fulfilled either the 2015 Movement Disorder Society clinical

diagnostic criteria (Postuma et al. 2015) or the UK Brain Bank criteria (Daniel and Lees 1993) for PD. Exclusion criteria included (i) atypical and secondary parkinsonism (*i.e.*, multiple system atrophy, progressive supranuclear palsy, brain injury, etc.); (ii) insufficient temporal bone window; and (iii) lack of full clinical assessments. We finally included 562 individuals, and 198 individuals without LID at baseline were successfully followed up every 3–6 mo (Fig. 1). The follow-up duration was determined from the baseline to the first occurrence of LID or, in the non-LID cases, from baseline to the last visit (the average follow-up duration was 37 mo). The investigation protocol was approved by the ethics committee of the Second Affiliated Hospital of Soochow University. Detailed clinical data including demographics were collected after written consent was obtained from all participants or their legally authorized representatives. All techniques were performed in accordance with the relevant guidelines and regulations.

### *Transcranial sonography*

Transcranial sonography examinations were performed according to our previous studies (Sheng et al. 2017; Li et al. 2020a) within 1 wk after the baseline clinical assessment. The brain was insonated through the right and left temporal bone windows in the axial plane by a sonographer using a 2.5-MHz sonographic device (Sequoia 512, Siemens Medical Solutions USA, Inc. 4V1C transducer) with a penetration depth of 14–16 cm and a dynamic range of 45–55 dB (Berg et al. 2008; Behnke et al. 2013). Image brightness, contrast and time-gain compensation were adapted as needed for best visualization (Berg et al. 2008; Behnke et al. 2013) (Fig. 2). The area of SN echogenicity was manually encircled with the cursor, and the planimetric area of SN and the mesencephalon was calculated automatically. TCS was performed in a darkened room by the same experienced clinician, who was blinded to the individuals' clinical status to eliminate any bias in the examination results.

The echogenicity of SN was divided into five grades (Bartova et al. 2008), where grade I = the same as brainstem; grade II = scattered points and thin lines slightly stronger than brainstem; grade III = patches of moderate echogenicity but weaker than brain pool; grade IV = patches of hyperechogenicity similar to brain pool; grade V = patches of hyperechogenicity stronger than brain pool. Grades I and II are defined as hypo-echogenicity (SN–), and grades III and V as SN+ (Berg et al. 2008). To quantitatively evaluate SN+, we measured the area of SN+ on the left and right sides and calculated the larger

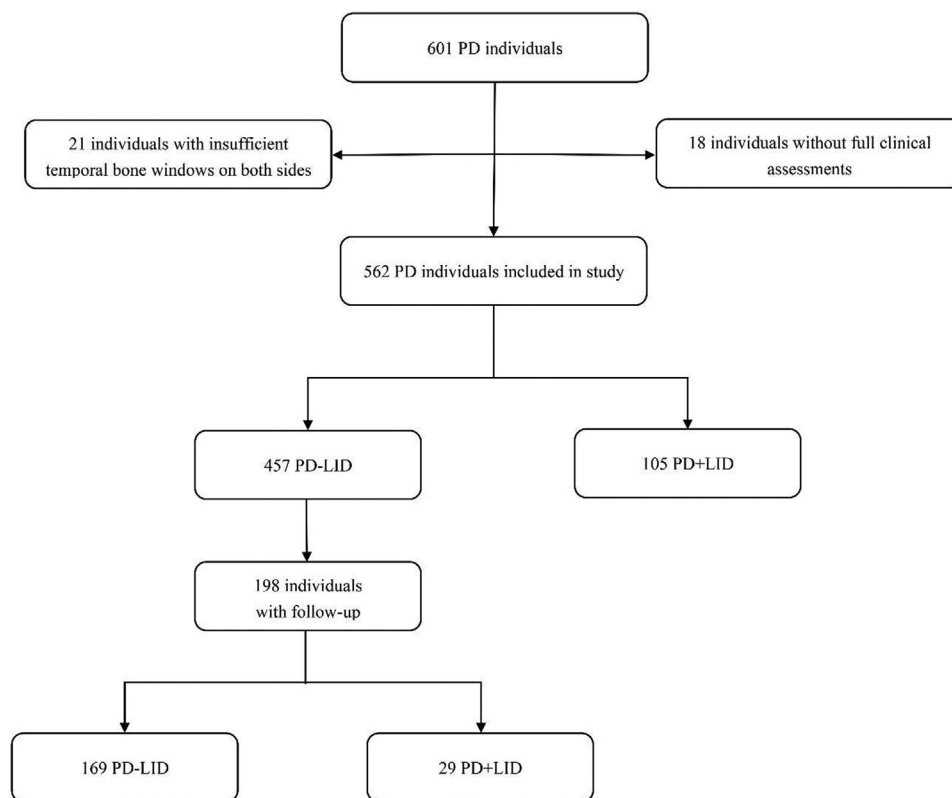


Fig. 1. Flowchart of included individuals.

area of SN+ of two sides ( $SN_L$ ), the total hyperecho-genic area of the SN on both sides ( $SN_T$ ) and the S/M ratio (defined as  $SN_T$  divided by the area of mesencephalon).

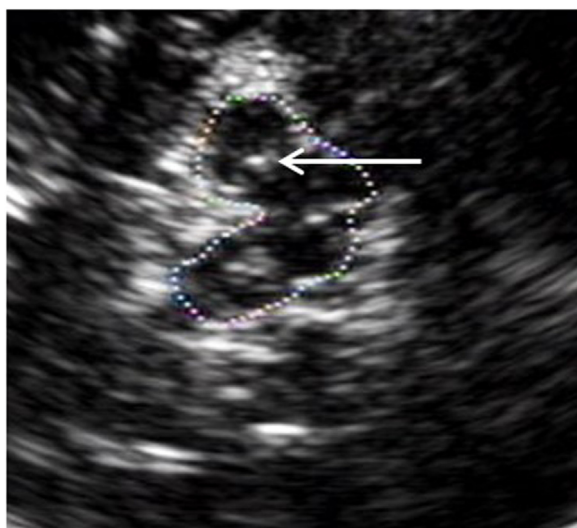


Fig. 2. Transcranial sonography image of individual with Parkinson disease. The *dotted area* represents mesencephalon, and the *white arrow*, substantia nigra.

#### Clinical assessments

All individuals included in our study underwent detailed clinical and neuropsychological tests at baseline and follow-up. Disease severity was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) (Martínez-Martín *et al.* 1994) and the Hoehn and Yahr scale (H–Y scale) (Goetz *et al.* 2004) in the “off state.” PD with LID was diagnosed if the UPDRS-IV dyskinesia score (items 32–35) was  $>0$ . The participants were divided into two groups: the PD with LID (PD+LID) group and the PD without LID (PD-LID) group. Levodopa-equivalent doses (LEDs) of medications were calculated as previously described (Tomlinson *et al.* 2010). Cognitive performance was evaluated using the Mini Mental State Examination (MMSE) (Folstein *et al.* 1975) and the Montreal Cognitive Assessment (MoCA, Beijing version) (Yu *et al.* 2012).

#### Statistical analysis

In univariate analyses, variables were tested for normality using the Kolmogorov–Smirnov test or Shapiro–Wilk test. Differences in metric variables between the groups were evaluated with Student's *t*-test or the Mann–Whitney *U*-test. Dichotomous variables were compared between groups with the  $\chi^2$ -test. Binary logistic regression of LID was used to assess the associations

among the demographic profiles, clinical assessments and  $SN_T$ . A binary logistic regression model with backward stepwise procedure was used to build a model for discriminating LID. The Hosmer–Lemeshow test was performed to assess the goodness of fit. Receiver-operating characteristic (ROC) curves and areas under the ROC curves (AUCs) were also determined. Kaplan–Meier (K–M) curves were constructed to illustrate the effect of  $SN_T$  and the predicted probability on LID. K–M curves were compared using the log-rank (Mantel–Cox) test. All statistical tests were two sided with  $p < 0.05$  as the threshold for statistical significance. All tests were performed using SPSS Statistics, version 26.0, 64-bit (IBM Corp., Armonk, NY, USA).

## RESULTS

### *Demographics and clinical assessments at baseline*

This study recruited 601 individuals with PD; 39 individuals were then excluded (Fig. 1). Therefore, 562 individuals were included in the analysis. At baseline, 105 individuals (18.7%) had experienced LID. Table 1 outlines the demographic variables and clinical assessments in the PD-LID and PD+LID groups. Sex composition and age did not significantly differ between the two groups ( $p = 0.266$  and  $0.244$ , respectively). Compared with the PD-LID group, the PD+LID group had an earlier age at onset ( $p = 0.012$ ), longer disease duration ( $p < 0.001$ ), shorter education duration ( $p < 0.001$ ) and higher LEDs ( $p < 0.001$ ). With respect to disease severity, the PD+LID group had a more advanced H–Y scale ( $p < 0.001$ ) and higher UPDRS scores ( $p = 0.004$  for UPDRS-I,  $p < 0.001$  for UPDRS-II and  $p < 0.001$  for UPDRS-III, respectively). However, there were no

significant differences in cognitive performance between the two groups ( $p = 0.078$  for the MMSE and  $p = 0.082$  for the MoCA, respectively) (Table 1).

### *Quantitative SN+ evaluations between the PD-LID and PD+LID groups*

We detected 406 (72.2%) individuals with SN+, 316 in the PD-LID group and 90 in the PD+LID group. Compared with the PD-LID group, the D+LID group had a higher proportion of SN+ ( $p = 0.001$ ), larger  $SN_L$ , larger  $SN_T$  and higher S/M ratio ( $p < 0.001$ , respectively) (Table 2).

In Figure 3 are the ROC curves of the SN+ evaluations ( $SN_T$ ,  $SN_L$  and S/M ratio) for discriminating LID in individuals with PD. The ideal diagnostic threshold should yield the highest sum of sensitivity and specificity, and the point situated at the top left corner of the curve would be the best diagnostic cutoff value. Among three ROC curves, the curve of  $SN_T$  reached the highest AUC (0.657), and we marked the point in this curve for the cutoff value of  $0.315 \text{ cm}^2$ . At this point, the sensitivity was 71.4% and the specificity was 53.8%. Thus, we included  $SN_T$  in our further analysis.

### *Independent risk factors associated with LID*

Table 3 outlines the results of binary logistic regression analysis of the risk factors and  $SN_T$  in the PD-LID and PD+LID groups. Following binary logistic regression analysis, we found that disease duration (odds ratio [OR] = 1.015, 95% confidence interval [CI]: 1.003–1.026,  $p = 0.014$ ), education duration (OR = 0.923, 95% CI: 0.865–0.984,  $p = 0.015$ ), LEDs (OR = 1.003, 95% CI: 1.002–1.004,  $p < 0.001$ ) and UPDRS-III score (OR = 1.026, 95% CI: 1.003–1.049,

Table 1. Demographic variables and clinical assessments in the PD-LID and PD+LID groups at baseline

	Total (n = 562)	PD-LID (n = 457)	PD+LID (n = 105)	p Value
Sex (male)	370 (65.8%)	296 (64.8%)	74 (70.5%)	0.266*
Age (y)	61.4 ± 9.8	61.2 ± 9.9	62.4 ± 9.6	0.244†
Age at onset (y)	57.5 ± 9.8	58.0 ± 9.8	55.3 ± 9.9	0.012‡
Disease duration (mo)	48.2 ± 44.2	38.8 ± 34.9	89.0 ± 56.0	<0.001†
Education duration (y)	7.4 ± 4.6	7.8 ± 4.6	5.7 ± 4.3	<0.001†
LEDs (mg)	422.0 ± 241.6	376.7 ± 203.9	619.5 ± 290.0	<0.001†
Hoehn and Yahr scale (“off” state)	2.1 ± 0.8	2.0 ± 0.7	2.5 ± 0.9	<0.001†
UPDRS-I	2.7 ± 2.0	2.6 ± 2.0	3.2 ± 2.1	0.004†
UPDRS-II	10.2 ± 6.3	9.3 ± 5.4	14.1 ± 8.1	<0.001†
UPDRS-III (“off” state)	23.1 ± 12.8	21.5 ± 11.4	30.1 ± 15.8	<0.001†
MMSE	25.1 ± 4.4	25.2 ± 4.3	24.6 ± 4.5	0.078†
MoCA	21.0 ± 5.1	21.2 ± 5.0	20.2 ± 5.2	0.082‡
$SN_T$ ( $\text{cm}^2$ )	0.39 ± 0.36	0.35 ± 0.34	0.55 ± 0.37	<0.001†

LID = levodopa-induced dyskinesia; LEDs = levodopa-equivalent doses; PD = Parkinson disease; PD+LID = PD with LID; PD-LID = PID without LID; MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Examination;  $SN_T$  = total hyperechogenic area of the substantia nigra on both sides; UPDRS = Unified Parkinson’s Disease Rating Scale.

Values are expressed as the number (%) or mean ± standard deviation.

\*  $p$  Value estimated using the  $\chi^2$ -test.

†  $p$  Values estimated using the Mann–Whitney  $U$ -test.

‡  $p$  Values estimated using the  $t$ -test.

Table 2. SN+ evaluations in the PD-LID and PD+LID groups

	Total (n = 562)	PD-LID (n = 457)	PD+LID (n = 105)	p Value
SN+	406 (72.2%)	316 (69.1%)	90 (85.7%)	0.001*
SN <sub>L</sub> (cm <sup>2</sup> )	0.28 ± 0.23	0.25 ± 0.22	0.37 ± 0.22	<0.001†
SN <sub>T</sub> (cm <sup>2</sup> )	0.39 ± 0.36	0.35 ± 0.34	0.55 ± 0.37	<0.001†
S/M ratio	9.4% ± 22.7%	7.6% ± 7.9%	17.3% ± 61.7%	<0.001†

PD+LID = PD with LID; PD-LID = PID without LID; SN+ = substantia nigra hyperechogenicity; SN<sub>L</sub> = the larger area of SN+ on both sides; SN<sub>T</sub> = total hyperechogenic area of the substantia nigra on both sides; S/M ratio = SN<sub>T</sub> divided by the area of midbrain.

Values are expressed as the number (%) or mean ± standard deviation.

\* p Value estimated using the  $\chi^2$ -test.

† p Values estimated using the Mann–Whitney U-test.

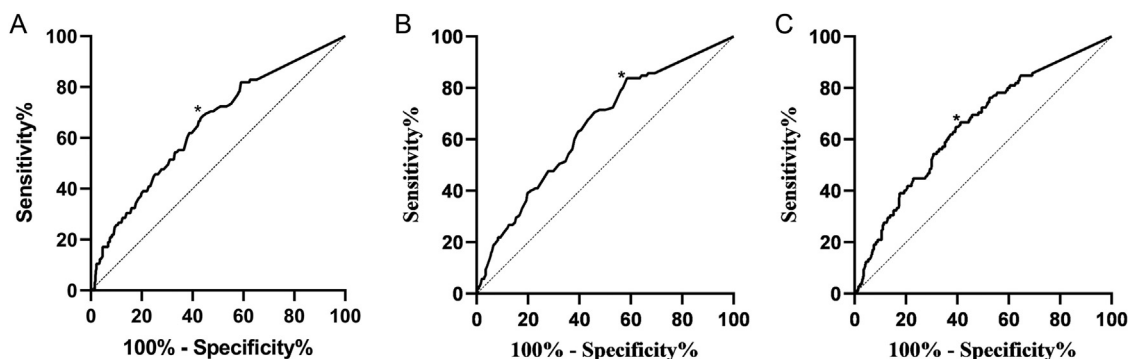


Fig. 3. (A) ROC curve of SN<sub>T</sub> for discriminating LID. Asterisk marks the point in the SN<sub>T</sub> curve for the cutoff of 0.315 cm<sup>2</sup>. At this point, the sensitivity value was 71.4%, and the specificity value was 53.8%. The AUC was 0.657 (95% CI: 0.599–0.715, *p* < 0.001). (B) ROC curve of SN<sub>L</sub> for discriminating LID. The asterisk marks the point in the SN<sub>L</sub> curve for the cutoff of 0.205 cm<sup>2</sup>. At this point, the sensitivity value was 83.8%, and the specificity value was 41.6%. The AUC was 0.650 (95% CI: 0.592–0.707, *p* < 0.001). (C) ROC curve of S/M ratio for discriminating LID. The asterisk marks the point in the SN<sub>T</sub> curve for the cutoff of 7.97%. At this point, the sensitivity value was 66.7%, and the specificity value was 58.9%. The AUC was 0.654 (95% CI: 0.596–0.712, *p* < 0.001). AUC = area under the ROC curve; CI = confidence interval; LID = levodopa-induced dyskinesia; ROC = receiver operating characteristic; S/M = SN<sub>T</sub> divided by the area of mesencephalon; SN = substantia nigra; SN<sub>L</sub> = larger area of SN of two sides; SN<sub>T</sub> = total hyperechogenic area of the SN on both sides.

*p* = 0.026) were independently associated with LID. After adjustments for sex, age, age at onset, disease duration, education duration, treatment, disease severity and

cognitive performance, the SN<sub>T</sub> was found to be significantly larger in the PD+LID group (OR = 2.601, 95% CI: 1.267–5.337, *p* = 0.009) (Table 3).

Table 3. Binary logistic regression of risk factors and SN<sub>T</sub> in the PD-LID and PD+LID groups

	PD-LID (n = 457)	PD+LID (n = 105)	Odds ratio (95% CI)	p Value*
Sex (male)	296 (64.8%)	74 (70.5%)	0.863 (0.474–1.571)	0.630
Age (y)	61.2 ± 9.9	62.4 ± 9.6	1.003 (0.884–1.138)	0.962
Age at onset (y)	58.0 ± 9.8	55.3 ± 9.9	0.975 (0.856–1.111)	0.706
Disease duration (mo)	38.8 ± 34.9	89.0 ± 56.0	1.015 (1.003–1.026)	0.014
Education duration (y)	7.8 ± 4.6	5.7 ± 4.3	0.923 (0.865–0.984)	0.015
LEDs (mg)	376.7 ± 203.9	619.5 ± 290.0	1.003 (1.002–1.004)	<0.001
UPDRS-III (“off” state)	21.5 ± 11.4	30.1 ± 15.8	1.026 (1.003–1.049)	0.026
MoCA	21.2 ± 5.0	20.2 ± 5.2	0.985 (0.930–1.043)	0.599
SN <sub>T</sub> (cm <sup>2</sup> )	0.35 ± 0.34	0.55 ± 0.37	2.601 (1.267–5.337)	0.009

CI = confidence interval; LID = levodopa-induced dyskinesia; LEDs = levodopa-equivalent doses; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; PD+LID = PD with LID; PD-LID = PID without LID; SN<sub>T</sub> = total hyperechogenic area of the substantia nigra on both sides; UPDRS = Unified Parkinson’s Disease Rating Scale.

The UPDRS score and Hoehn and Yahr scale were synergistic, and the MoCA and Mini Mental State Examination were synergistic, so only the UPDRS-III score and MoCA were included for analysis.

Values are expressed as the number (%) or mean ± standard deviation unless otherwise noted.

\* p Values were estimated from binary logistic regression models adjusted for sex, age, age at onset, disease duration, education duration, LEDs, UPDRS-III and MoCA.

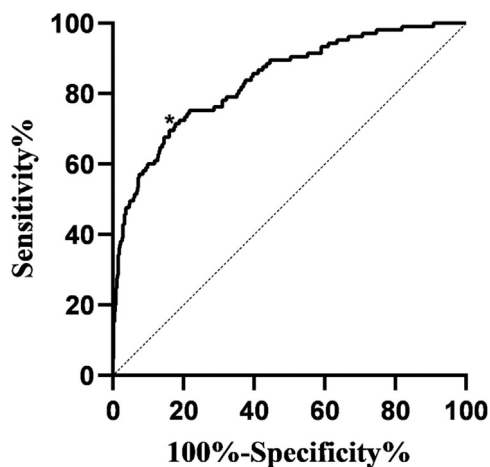


Fig. 4. Receiver operating characteristic curve of predicted probability for discriminating levodopa-induced dyskinesia in individuals with Parkinson disease. The predicted probability was used to plot the receiver operating characteristic curve. The predicted probability was calculated with the prediction model, established by binary logistic regression analysis with the backward stepwise procedure using disease duration, education duration, levodopa-equivalent doses, Unified Parkinson's Disease Rating Scale-III score and  $SN_T$ . The asterisk marks the point in the model curve for the cutoff of 0.2025. At this point, the sensitivity value was 71.4%, and the specificity value was 82.3%. The area under the receiver operating characteristic curve was 0.839 (95% confidence interval: 0.795–0.883,  $p < 0.001$ ).  $SN_T$  = total hyperechogenic area of the SN on both sides.

#### Development of model for discriminating LID

The above-mentioned associated risk factors, including disease duration, education duration, LEDs, UPDRS-III score and  $SN_T$ , were included in the binary logistic regression analysis with the backward stepwise procedure. Figure 4 illustrates the ROC curve of the probability for discriminating LID, which indicates that the AUC was 0.839 (95% CI: 0.795–0.883,  $p < 0.001$ ) with an acceptable goodness of fit (Hosmer–Lemeshow,  $p > 0.05$ ). We also marked the point in the curve for the cutoff value of 0.2025. At this point, the sensitivity was 71.4%, and the specificity was 82.3% (Fig. 4).

#### Confirmation of $SN_T$ and the prediction model with follow-up

We successfully followed up 198 individuals from the PD-LID group at baseline; the average follow-up duration was 37 mo, and 29 individuals (14.6%) developed LID during the follow-up. We first divided 198 patients into two groups, according to the  $SN_T$  cutoff value (0.315  $cm^2$ ). Follow-up duration, change in LEDs and UPDRS-III score between follow-up and baseline did not significantly differ between the two groups (Table 4). From the K–M curves, individuals with a larger  $SN_T$  were more likely to develop LID as compared with individuals with a smaller  $SN_T$  (Fig. 5).

We then divided 198 patients according to the baseline-predicted probability cutoff value (0.2025). Follow-up duration, change in LEDs and UPDRS-III score between the follow-up and baseline groups did not significantly differ between the two groups (Table 5). From the K–M curves, individuals with a higher predicted probability were more likely to develop LID as compared with individuals with a lower predicted probability (Fig. 6).

## DISCUSSION

Levodopa-induced dyskinesia is a common motor complication of PD that is often caused by levodopa treatment (Chen et al. 2020). The prevalence of LID varies from 10% to 40% in different studies depending on the progression of the disease (Manson et al. 2012; Tran et al. 2018; Turcano et al. 2018; Kelly et al. 2019). In the present study, the incidence was 18.7%, which is consistent with previous studies (Manson et al. 2012; Tran et al. 2018; Turcano et al. 2018; Kelly et al. 2019). LID may greatly affect the quality of life of individuals with PD and their families; therefore, discriminating individuals at higher risk of LID may be of importance. In this study, using binary logistic regression analysis, we found that disease duration, education duration, LEDs and disease severity were independent risk factors for LID, which is consistent with previous studies (Sharma et al. 2010; Walker et al. 2011; Manson et al. 2012; Warren Olanow et al. 2013; Tran et al. 2018; Luca et al. 2021).

Table 4. Clinical assessments at follow-up (grouped by  $SN_T$ )

	Total (n = 198)	$SN_T < 0.315$ (n = 118)	$SN_T \geq 0.315$ (n = 80)	p Value
Follow-up duration (mo)	37.1 ± 18.7	38.9 ± 19.2	34.4 ± 17.8	0.055*
Change in LEDs (mg)	68.7 ± 179.7	62.8 ± 184.8	77.3 ± 172.7	0.896*
Change in UPDRS-III	2.4 ± 11.4	3.2 ± 12.6	1.3 ± 9.3	0.189*
LID during follow-up	29 (14.6%)	11 (9.3%)	18 (22.5%)	0.010†

LEDs = levodopa-equivalent doses; LID = levodopa-induced dyskinesia;  $SN_T$  = total hyperechogenic area of the substantia nigra on both sides; UPDRS = Unified Parkinson's Disease Rating Scale.

Values are expressed as the number (%) or mean ± standard deviation.

\* p Values estimated between two groups using the Mann–Whitney U-test.

† p Value estimated between two groups using the  $\chi^2$ -test.

Table 5. Clinical assessments at follow-up (grouped by predicted probability)

	Total (n = 198)	Predicted probability <0.2025 (n = 167)	Predicted probability $\geq$ 0.2025 (n = 31)	<i>p</i> Value
Follow-up duration (mo)	37.1 $\pm$ 18.7	37.6 $\pm$ 19.0	34.4 $\pm$ 17.4	0.407*
Change in LEDs (mg)	68.7 $\pm$ 179.7	76.0 $\pm$ 184.3	29.1 $\pm$ 190.5	0.335*
Change in UPDRS-III	2.4 $\pm$ 11.4	2.7 $\pm$ 11.0	0.6 $\pm$ 13.4	0.110*
LID during follow-up	29 (14.6%)	19 (11.4%)	10 (32.3%)	0.003 <sup>†</sup>

LEDs = levodopa-equivalent doses; LID = levodopa-induced dyskinesia; UPDRS = Unified Parkinson's Disease Rating Scale.

\* *p* Values estimated between two groups using the Mann–Whitney *U*-test.

<sup>†</sup> *p* Value estimated between two groups using the  $\chi^2$ -test.

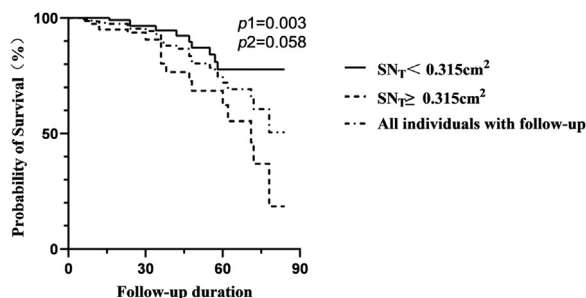


Fig. 5. Kaplan–Meier curves of developing levodopa-induced dyskinesia during follow-up (grouped by  $SN_T$ ). *p* Values were estimated using the log-rank test:  $p_1$  = comparison between the  $SN_T < 0.315$  and  $SN_T \geq 0.315$  groups;  $p_2$  = comparison between the  $SN_T \geq 0.315$  group and all individuals followed up.  $SN_T$  = total hyperchogenic area of the SN on both sides.

In our study, all 562 individuals underwent TCS. In total, we found 406 (72.2%) individuals with  $SN+$ , which is consistent with our previous study (Li *et al.* 2020a). The proportions of  $SN+$  reported in other studies ranged from 60% to 80% (Yu *et al.* 2018; Zhou *et al.* 2018); this difference may be due to different components, diagnostic criteria and the operator. Therefore, because of its convenience and high diagnostic value, TCS currently has a wide range of applications in

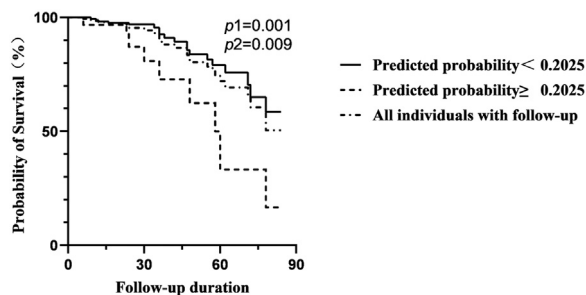


Fig. 6. Kaplan–Meier curves of developing levodopa-induced dyskinesia during follow-up (grouped by predicted probability). *p* Values were estimated using the log-rank test:  $p_1$  = comparison between the predicted probability <0.2025 group and the predicted probability  $\geq$ 0.2025 group;  $p_2$  = comparison between the predicted probability  $\geq$ 0.2025 group and all individuals followed up.

various movement disorders, especially in individuals without obvious motor symptoms.

We quantitatively analyzed the association between  $SN+$  (detected by TCS) and LID in individuals with PD. Sex, age, age at onset, disease duration, education duration, treatment, disease severity and cognitive performance were included as covariates. We found that individuals with PD+LID had significantly larger  $SN_T$  compared with individuals with PD-LID. We then constructed an ROC curve of  $SN_T$  and detected moderate sensitivity (71.4%) and specificity (53.8%); the AUC was 0.657. We further established a model including four independent risk factors (disease duration, education duration, LEDs and UPDRS-III score) and  $SN_T$ . The sensitivity and specificity of our model were 71.4% and 82.3%, and the AUC reached 0.839, which indicated the credibility and validity of our established model. In addition, our findings were also validated by follow-up observations, where individuals with a larger  $SN_T$  or a higher predicted probability were more likely to develop LID during follow-up. These findings indicated that the quantitative characteristics of  $SN+$  had good values in discriminating LID to a certain extent, which had not been reported before and may also increase the scope of the application of TCS in PD.

To date, the detailed mechanism causing  $SN+$  and the causal relationship between  $SN+$  and LID remain unknown. However, abnormal iron deposition has been reported to be associated with  $SN+$  (Berg *et al.* 2001, 2008), which may provide some clues to understanding the detailed mechanism underlying  $SN+$ . Interestingly, excessive iron deposition may lead to abnormal oxidative stress in the brain, which could result in dopaminergic neuron degeneration and death (Gaasch *et al.* 2007; Berg *et al.* 2010; Carta *et al.* 2017; Zhang *et al.* 2020). Nigrostriatal pathology may then further increase the risk of LID. Functional analyses are warranted in the future for further clarification.

To our knowledge, this is the first study to investigate the association between the hyperchogenic area of the SN and LID in individuals with PD. In addition, we provided an effective tool that is helpful in discriminating LID. However, our study has some limitations. First, our

sample size was relatively small. Second, our patients were from one center. Further studies with a larger sample size and in different populations are warranted.

## CONCLUSIONS

This study found that quantitative TCS evaluations of SN+ are associated with LID and are useful in predicting LID in individuals with PD.

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*Conflict of interest disclosure*—The authors declare no competing interests.

*Data availability statement*—The data that support the findings of this study are available from the corresponding author on reasonable request.

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