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Dysregulation of Circulatory Levels of lncRNAs in Parkinson's Disease

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Abstract

Emerging evidence suggested that long non-coding RNAs (lncRNAs) were involved in Parkinson's disease (PD) pathogenesis. Herein, we used gene expression profiles from GEO database to construct a PD-specific ceRNA network. Functional enrichment analysis suggested that ceRNA network might participate in the development of PD. PPI networks were constructed, and the ceRNA subnetwork based on five hub genes was set up. In a cohort of 32 PD patients and 31 healthy controls, the expression of 10 DElncRNAs (TTC3-AS1, LINC01259, ZMYND10-AS1, CHRM3-AS1, MYO16-AS1, AGBL5-IT1, HOTAIRM1, RABGAP1L-IT1, HLCS-IT1, and LINC00393) were further verified. Consistent with the microarray data, LINC01259 expression was significantly lower in PD patients compared with controls ($P=0.008$). Intriguingly, such a difference was only observed among male patients and male controls when dividing study participants based on their gender ($P=0.016$). However, the expression of other lncRNAs did not differ significantly between the two groups. Receiver operating characteristic (ROC) curve analysis revealed that the diagnostic power of LINC01259 was 0.694 for PD and 0.677 for early-stage PD. GSEA enrichment analysis revealed that LINC01259 was mainly enriched in biological processes associated with immune function and inflammatory response. Moreover, LINC01259 expression was not correlated with age of patients, disease duration, disease stage, MDS-UPDRS score, MDS-UPDRS III score, MMSE score, and MOCA score. The current study provides further evidence for the dysregulation of lncRNAs in circulating leukocytes of PD patients, revealing that LINC01259 has clinical potential as a novel immune and inflammatory biomarker for PD and early-stage PD diagnosis.

Keywords Parkinson's disease · Long non-coding RNA · Competing endogenous RNA · Circulating leukocytes · ROC curve

Introduction

Parkinson's disease (PD), one of the most common progressive neurodegenerative disorders, affects 2–3% of the population ≥ 65 years of age [1]. Misfolding and abnormal aggregation of α-synuclein (α-syn) is the main cause of progressive and selective death of dopaminergic neurons in the substantia nigra pars compacta, leading to the occurrence of clinical symptoms [2]. Although the clinical diagnosis relies on the presence of major motor symptoms (bradykinesia, resting tremor, rigidity, and postural instability), many non-motor symptoms occur prior to the hallmark clinical motor symptoms, thereby greatly reducing the quality of life in PD [3–5]. However, the essential molecular mechanism underlying PD remains largely unknown. Therefore, further elucidating the pathogenesis of PD and finding new biomarkers to improve the diagnosis and evaluation of PD are needed urgently.

Long non-coding RNAs (lncRNAs) are a category of non-coding RNAs (ncRNAs) with lengths exceeding 200 nucleotides, which are the most numerous among ncRNAs [6]. By interacting with DNA, RNA, and proteins, lncRNAs hold significant promise as crucial players with diverse biological functions, such as modulating chromatin function, regulating the assembly and function of organelles and nuclear

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condensates, altering the stability and translation of cytoplasmic mRNAs, and interfering with signaling pathways [7, 8]. Importantly, lncRNAs can regulate target mRNA expression by combining shared miRNAs based on the competitive endogenous RNAs (ceRNA) hypothesis [8]. Numerous studies also suggested that lncRNAs are represented as specific cell and subcell types in different regions of the brain and are extensively expressed in the central nervous system (CNS) [9, 10]. Therefore, lncRNAs are increasingly regarded as indispensable molecules in the occurrence and development of aging-related neurodegenerative diseases, including PD, Alzheimer's disease (AD), and Huntington's disease (HD). Nevertheless, little is known about their specific role in the PD-specific lncRNA-miRNA-mRNA ceRNA network.

Although α-syn has been extensively investigated in peripheral circulation as a central player in PD pathogenesis and pathology, the exact role of mutant α-syn in PD pathology remains unclear. Several recent studies have demonstrated that lncRNAs might contribute to PD pathogenesis by regulating the expression and aggregation of α-syn [11–15]. In human neuroblastoma SH-SY5Y cells, lncRNA SNHG1 promotes α-syn aggregation and toxicity by targeting miR-15b-5p to activate SIAH1 [13]. Elsewhere, the upregulation of lincRNA-p21 could indirectly increase the expression of α-syn by targeting miR-1277-5p to suppress viability and activate apoptosis [14]. Recent research has revealed that lncRNA OIP5-AS1 reduces α-syn aggregation by sponging miR-126 to activate PLK2 [15]. Meanwhile, these findings also confirmed that lncRNAs could facilitate the apoptosis and autophagy of dopaminergic neurons, raising the possibility that they may be involved in PD [14, 15].

The occurrence and progression of PD is a complicated process accompanied by neuroinflammation and increased systemic inflammation as well as blood–brain barrier (BBB) disruption [16–18]. α-Syn accumulation in the central nervous system could activate astrocytes and microglia, which leads to chronic neuroinflammation [19]. In the peripheral circulation, leukocytes are key effector cells within the inflammatory immune reaction that sustain the detrimental response in the CNS and systemic inflammatory responses by producing proinflammatory cytokines [20]. The release of proinflammatory cytokines can further promote the activation of leukocytes and microglia and the death of neural cells. Furthermore, the BBB may become even more compromised as a result of the production of proinflammatory cytokines, leading to wider contact between the CNS and peripheral system [21]. Indeed, quantitative and qualitative changes in circulating leukocytes and their subpopulations have already been described in clinical PD. Previous research has shown the increase of neutrophils and the decrease of lymphocytes in PD patients [22–24]. Additionally, peripheral immune cells (e.g., Th cells, CD3 + T cells, and CD4 + T cells) are highly neurotoxic, indicating that they may be another key mediator of chronic neuroinflammation and peripheral adaptive immunity in PD [25, 26]. Notably, the infiltration of peripheral immune cells can also suppress inflammation of the CNS and promote tissue repair [27]. Meanwhile, there is growing evidence that lncRNAs can activate innate and adaptive immune responses by participating in immune cell activation, differentiation, regulation of transcription and epigenetics, and cell signaling [28, 29]. Recent studies have demonstrated that lncRNA H19 promotes leukocyte inflammation in cerebral ischemic stroke by targeting the miR-29b/C1QTNF6 axis [30]. However, only a few studies explored the dysregulation of lncRNAs in circulating leukocytes of PD patients [31–34]. In view of this, we hypothesized that lncRNAs in peripheral blood leukocytes may play an essential role in PD pathogenesis through PD-specific ceRNA regulatory networks.

In this study, we used gene expression profiles from the Gene Expression Omnibus database (GEO) to construct a PD-specific lncRNA-miRNA-mRNA ceRNA network. Next, we investigated the potential biological functions and pathological mechanisms of miRNAs and differentially expressed mRNAs (DEmRNAs) in the ceRNA network and constructed a subnetwork centered on the hub genes to explore their relationship. Further, we verified 10 differentially expressed lncRNAs (DElncRNAs) in the ceRNA network in 32 PD patients and 31 healthy controls (HC) and identified the downregulation of LINC01259 in PD patients. Finally, we explored the correlation between LINC01259 expression and disease severity as well as cognitive ability and further investigated the biological function of LINC01259 using Gene Set Enrichment Analysis (GSEA). We aimed to find PD-related biomarkers for revealing disease pathogenesis by analyzing the expression levels of lncRNAs in the peripheral blood leukocytes of PD patients.

Materials and Methods

Data Collection

The GEO database is a public functional genomic database that allows users to query and download experiments and curated gene expression profiles (https://www.ncbi.nlm.nih.gov/) [35]. The normalized expression profile of GSE133347 was obtained from GEO database using the "GEOquery" R package [36]. GSE133347 consisted of 5 blood samples from PD patients and 5 blood samples from age and sex-matched HC. Exclusion criteria for PD were as follows: (1) the presence of other neurologic illness or injury (traumatic brain injury, stroke, epilepsy); (2) the presence of chronic inflammatory disease; (3) the presence of previous malignancies or cardiac events; and (4) unstable psychiatric disorders such

as schizophrenia or major depression. Total circulating leukocyte RNA was obtained from EDTA-treated whole blood, and the microarray assays were performed on the platform of Agilent-074348 Human LncRNA v6 4X180K (GPL21047, Probe Name Version) to detect the lncRNA and mRNA expression profiles of circulating leukocytes. Details of sample collection, RNA extraction, and microarray analysis are described in Supplementary Material 1.

Identification of Differentially Expressed RNAs

Based on the criteria of the absolute value of log2 fold change (|logFC|) > 0.5 and *P*-value < 0.05, the limma package [37] in R software was used to identify DElncRNAs and DEmRNAs between PD patients and HC. Heatmaps of DElncRNAs and DEmRNAs were plotted using the heatmap packages in R software. |logFC|> 0.5 and $P < 0.05$ were considered statistically significant.

CeRNA Network Construction

The ceRNA network was established based on the associations between lncRNAs-miRNAs and miRNAs-mRNAs. Firstly, DElncRNAs were selected to predict miRNAs through the starBase database [38], and the lncRNA-miRNA interactions were established. To further investigate the functions of DElncRNA, TargetScan [39], miRTarBase [40], and miRDB [41] databases analysis was applied to find the key target genes of miRNAs. Then, these DEmRNAs in the ceRNA network construction were identified by intersecting DEmRNAs from GEO database with these intersecting mRNAs obtained by three prediction methods and further integrated miRNA-mRNA interactions. Finally, the PD-specific ceRNA network was constructed based on the "ceRNA hypothesis." Cytoscape software (version 3.7.2) [42] was used to visualize the relationships of the ceRNA network.

Functional Enrichment Analysis

The Gene Ontology (GO) functional enrichment analysis was usually performed to describe gene functions in terms of biological process (BP), cellular component (CC), and molecular function (MF). To screen for possible functions of DEmRNAs in the ceRNA network, GO analysis was conducted using the "clusterProfiler" package [43] in R with "$P < 0.05$" as the cutoff criteria for weeding out the enriched GO terms. Additionally, underlying functions of miRNAs extracted from the ceRNA network were explored by TAM 2.0 online tool (http://www.lirmed.com/tam2/) ($P < 0.05$).

Protein–Protein Interaction (PPI) Networks Construction and Identification of Hub Genes

The PPI networks of DEmRNAs in the ceRNA network were constructed using the Search Tool for the Retrieval of Interacting Genes (STRING) database [44] with a combined score ≥ 0.4. CytoHubba plugin [45] of Cytoscape 3.7.2 was used to visualize the PPI networks. Then, the maximal clique centrality (MCC) algorithm was implemented to identify hub genes among the above differentially expressed genes (DEGs).

Subject Recruitment and Blood Sample Collection

Fasting blood samples were collected from 32 PD patients (in the "off" medication state) and 31 HC between 6 and 9 am on an empty stomach. All subjects were Chinese and were recruited from the Nanjing First Hospital. Demographic data for all subjects are summarized in Table 1. The diagnosis of idiopathic Parkinson's disease (IPD) was fulfilled with the International Parkinson and Movement

Table 1 Clinical characteristics of PD patients and HC for quantitative PCR

Characteristics	PD patients	HC	*P* value
Total number of subjects	32	31	NA
Male (%)	17 (53.13%)	19 (61.29%)	0.513
Age (y)	65.47 ± 10.125	62.97 ± 11.038	0.352
WBC count (10^9/L)	5.43 ± 1.077	5.69 ± 1.724	0.469
RBC count (10^{12}/L)	4.45 ± 0.461	4.48 ± 0.479	0.798
Disease duration (y)	5.92 ± 3.807	NA	NA
H-Y stage (off)	2.23 ± 0.729	NA	NA
Early stage: 1–2.5 (%)	29 (90.63%)	NA	NA
1	2 (6.25%)	NA	NA
1.5	1 (3.13%)	NA	NA
2	18 (56.25%)	NA	NA
2.5	8 (25%)	NA	NA
Late stage: 3–5 (%)	3 (9.38%)	NA	NA
3	1 (3.13%)	NA	NA
4	1 (3.13%)	NA	NA
5	1 (3.13%)	NA	NA
MDS-UPDRS III (off)	32.37 ± 14.100	NA	NA
MDS-UPDRS (off)	51.22 ± 24.270	NA	NA
MMSE (off)	25.69 ± 4.700	NA	NA
MOCA (off)	20.25 ± 5.946	NA	NA

PD Parkinson's disease, *HC* healthy controls, *WBC* white blood cells, *RBC* red blood cells, *H-Y stage* Hoehn-Yahr stage, *MDS-UPDRS III score* Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III score, *MDS-UPDRS total scores* Movement Disorder Society-Unified Parkinson's Disease Rating Scale part total scores, *MMSE* Mini-Mental State Examination, *MOCA* Montreal Cognitive Assessment; *off* in the "off" medication state (≥ 12 h after last dopaminergic medication)

Disorder Society (MDS) clinical diagnostic criteria for PD [46]. Exclusion criteria included (1) atypical or secondary parkinsonism; (2) other neurologic illness or injury (traumatic brain injury, ischemic/hemorrhagic stroke, Alzheimer's disease, epilepsy); (3) acute or chronic inflammatory diseases; (4) cardiovascular disease or previous malignancies; and (5) unstable psychiatric disorders such as schizophrenia or major depression. Individuals enrolled in the HC group were cognitively normal, free of neurological disorders, and with no family history of PD. Additionally, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [47] and Hoehn-Yahr stage (H-Y stage) [48] were used to evaluate the severity and progression of PD, as well as functional disability associated with PD. The Mini-Mental State Examination (MMSE) [49] and Montreal Cognitive Assessment (MOCA) [50] were administered to PD patients to estimate their cognitive level. All clinical scales for PD patients were assessed in the "off" medication state (≥ 12 h after last dopaminergic medication). The study was approved by the ethics committee of the Nanjing First Hospital, and informed consent was obtained from all study subjects.

Expression Assays

Red blood cells were removed immediately using the red blood cell lysis buffer (RT122, Tiangen, China). Total RNA was extracted from circulating leukocytes using RNAprep pure Blood Kit (DP433, Tiangen, China), and stored at − 80 °C until further use. Afterward, the isolated RNA was reverse transcribed into cDNA using the PrimeScript™ RT reagent Kit with gDNA Eraser (RR047A, TaKaRa, Japan) following the manufacturer's instructions. Quantitative PCR was performed using TB Green® Premix Ex Taq™ (RR420A, TaKaRa, Japan) and ABI QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA). Specific primers used for the reaction are as follows: TTC3-AS1-F, 5′-aggcttctgcttgtgactcc-3′, TTC3-AS1-R, 5′-ggagaaatgggaaagtggtttga-3′; LINC01259-F, 5′-tcatcatgactgccagagagg-3′, LINC01259-R2, 5′-ttcagaaggtggtcccacaa-3′; ZMYND10-AS1-F, 5′-tggaggccagctttactgtg-3′, ZMYND10-AS1-R, 5′-cgatatgggagacttcctgcc-3′; CHRM3-AS1-F, 5′-actcggagaacgacctctct-3′, CHRM3-AS1-R, 5′-gatatcctccgcgaactgcat-3′; MYO16-AS1-F, 5′-gggattggctcttgcttcct-3′, MYO16-AS1-R, 5′-agtcagaatcaactgtgtccca-3′; AGBL5-IT1-F, 5′-gctcttaactcatagttcctggg-3′, AGBL5-IT1-R, 5′-ccagtgacaacctagaaaaagctc-3′; HOTAIRM1-F, 5′-ttgggggtttctgtaggcac-3′, HOTAIRM1-R, 5′-agtgcacaggttcaagccat-3′; RABGAP1L-IT1-F, 5′-ttgggctaagacgagcctac-3′, RABGAP1L-IT1-R, 5′-agcttggcttaaatagatcagagg-3′; HLCS-IT1-F, 5′-gaagcggattggtggactg-3′, HLCS-IT1-R, 5′-tcccatctgccaggtcaataaa-3′; LINC00393-F, 5′-gaaatgtttggaggtcaactgc-3′, LINC00393-F, 5′-gtcttccagaggataatgccca-3′. Oligonucleotides to beta-actin transcripts were included as controls: Actin-F, 5′-ccttcctgggcatggagtc-3′, Actin-R, 5′-tgatcttcattgtgctgggtg-3′. All samples were run in technical triplicates. lncRNA expression relative to internal control was calculated by − ΔCt value (ΔCt = Ct mean beta-actin − Ct mean lncRNAs). As there is a positive correlation between − ΔCt and lncRNA expression level, higher − ΔCt values were accompanied by increased lncRNA expression.

GSEA

GSEA was performed to further examine the biological function of LINC01259. The GO.bp. v7. 5. symbols.gmt in the Molecular Signatures Database (MSigDB, http://broadinstitute.org/gsea/msigdb/index.jsp) was selected as the reference gene set, and the default weighted enrichment method was applied for 1000 enrichment analyses. Gene sets with $P < 0.05$ and FDR < 0.25 were considered significantly enriched gene sets.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 software (IBM Corp. Software, China). Categorical variables were presented as counts and percentages, and continuous variables were summarized as mean and standard deviation [M (± SD)] or median and interquartile range [M (P25–P75)] according to the normality of the distribution (checked using the Kolmogorov–Smirnov test). Two unpaired groups were analyzed using the two-tailed Student's *t*-test for normal distribution data and the two-tailed Mann–Whitney *U*-test for non-normal distribution data. Receiver operating characteristic (ROC) curves were plotted to assess the diagnostic power of DElncRNAs expression levels, and Youden's J parameter was measured to find the optimum threshold. Pearson or Pearson correlations were used to evaluate partial correlations between DElncRNAs expression levels and age of PD patients, disease duration, disease stage (H-Y stage), MDS-UPDRS score, MDS-UPDRS III score, MMSE score, and MOCA score. Two-sided *P*-values of < 0.05 were considered significant.

Results

DElncRNAs and DEmRNAs in PD

We analyzed the expression of DElncRNAs and DEmRNAs in circulating leukocytes between age and sex-matched 5 PD patients and 5 HC and plotted them on heatmaps (Fig. 1). The results show that 10 lncRNAs (four downregulated and six upregulated, Fig. 1a) and 418 mRNAs (196

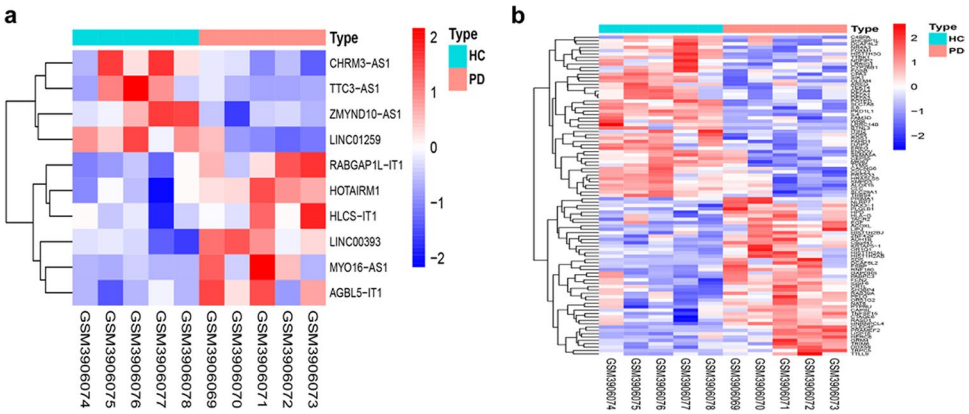

Fig. 1 Identification of DElncRNAs and DEmRNAs in PD patients and HC. **a** The heatmap of DElncRNAs. **b** The heatmap of DEmRNAs. Red and blue denote upregulated and downregulated RNAs, respectively. DElncRNAs, differentially expressed long non-coding RNAs; DEmRNAs, differentially expressed messenger RNAs; PD, Parkinson's disease; HC, healthy controls

Table 2 The expression of 10 DElncRNAs in PD from GEO database

ID	LogFC	*P* value*	Type
TTC3-AS1	− 2.39358	0.035424	Down
LINC01259	− 1.33416	0.004743	Down
ZMYND10-AS1	− 1.28634	0.009288	Down
CHRM3-AS1	− 1.28573	0.018787	Down
MYO16-AS1	2.482492	0.036127	Up
AGBL5-IT1	1.491257	0.01471	Up
HOTAIRM1	1.147397	0.005089	Up
RABGAP1L-IT1	1.110705	0.007404	Up
HLCS-IT1	1.081467	0.043879	Up
LINC00393	1.032343	0.003257	Up

*Significant difference, $P < 0.05$. *DElncRNAs* differentially expressed long non-coding RNA, *PD* Parkinson's disease, *GEO* the Gene Expression Omnibus database, *LogFC* log2 fold change

downregulated and 222 upregulated, Fig. 1b) were identified as differentially expressed RNAs in PD. All DElncRNAs and DEmRNAs with their names, logFC, and *P*-value are listed in Table 2 and Table S1, respectively.

Construction of the ceRNA Network in PD

We identified 62 DEmRNAs by intersecting 418 DEmRNAs from GEO database with these intersecting mRNAs obtained from three prediction databases. To further investigate how lncRNAs regulate mRNAs in PD, we constructed a lncRNA-miRNA-mRNA ceRNA network based on 10 DElncRNAs, 193 miRNAs, and 62 DEmRNAs using Cytoscape v3.7.2 (Fig. 2). All DElncRNAs, miRNAs and DEmRNA in the ceRNA network with their names are listed in Table S2.

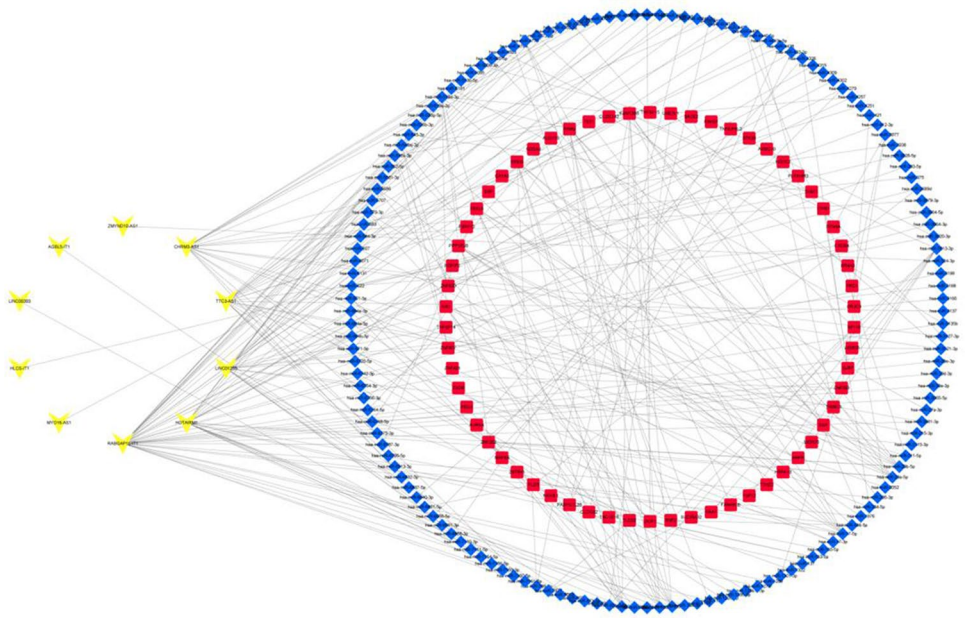

Fig. 2 Construction of lncRNA-miRNA-mRNA ceRNA network in PD. Yellow, blue, and red nodes represent DElncRNAs, miRNAs, and DEmRNAs, respectively. The gray lines represent interactions between RNAs. ceRNA, competing endogenous RNAs; PD, Parkinson's disease; DElncRNAs, differentially expressed long non-coding RNAs; miRNAs, microRNAs; DEmRNAs, differentially expressed messenger RNAs

Functional Enrichment Analysis

We explored the potential biological functions of mRNA and miRNA in the ceRNA network. GO analyses revealed that mRNAs in the ceRNA network were significantly associated with nine BPs, including regulation of DNA-binding transcription factor activity, regulation of cellular protein catabolic process, and intracellular receptor signaling pathway. The most enriched CC was microtubule, and the enrichment of MF was mainly related to ubiquitin-protein transferase activity (Fig. 3). And miRNAs in the ceRNA network were remarkably correlated with 13 BPs, including autophagy, neuron apoptosis, oxidative stress, and aging (Table 3). Functional enrichment analysis suggested that the PD-specific ceRNA network might participate in the occurrence and development of PD by regulating these biological processes and pathways.

PPI Networks Construction and Identification of Hub Genes

To identify the interactions between the proteins translated by the screened DEGs, PPI networks were constructed through the STRING database (Fig. 4a). After removing the unconnected nodes, a total of 19 protein nodes and 20 interaction pairs were found in the constructed PPI networks. Based on CytoHubba's MCC algorithm, we identified a hub gene network containing five nodes and 10 edges, revealing the critical roles of these five genes (AURKA, CDCA3, PRC1, SKA1, and RRM2) in PD (Fig. 4b). In addition, a ceRNA subnetwork based on five hub genes was set up (Fig. 4c).

Validation of the 10 DElncRNAs in 32 PD Patients and 31 HC by Quantitative PCR

We further verified the expression of 10 DElncRNAs (TTC3-AS1, LINC01259, ZMYND10-AS1, CHRM3-AS1, MYO16-AS1, AGBL5-IT1, HOTAIRM1, RABGAP1L-IT1, HLCS-IT1, and LINC00393) by quantitative PCR in 32 PD patients and 31 HC (Table S3). Consistent with the microarray data, LINC01259 expression was significantly lower in PD patients compared with HC (Fig. 5a). However, the expression of other lncRNAs was not significantly different in the two groups. Notably, the expression level of MYO16-AS1 was close to the limit of significant difference between the two groups ($P = 0.167$), and its expression trend in PD was consistent with the microarray data. Further analyses showed that LINC01259 expression was significantly different between male patients and male controls (Fig. 5b).

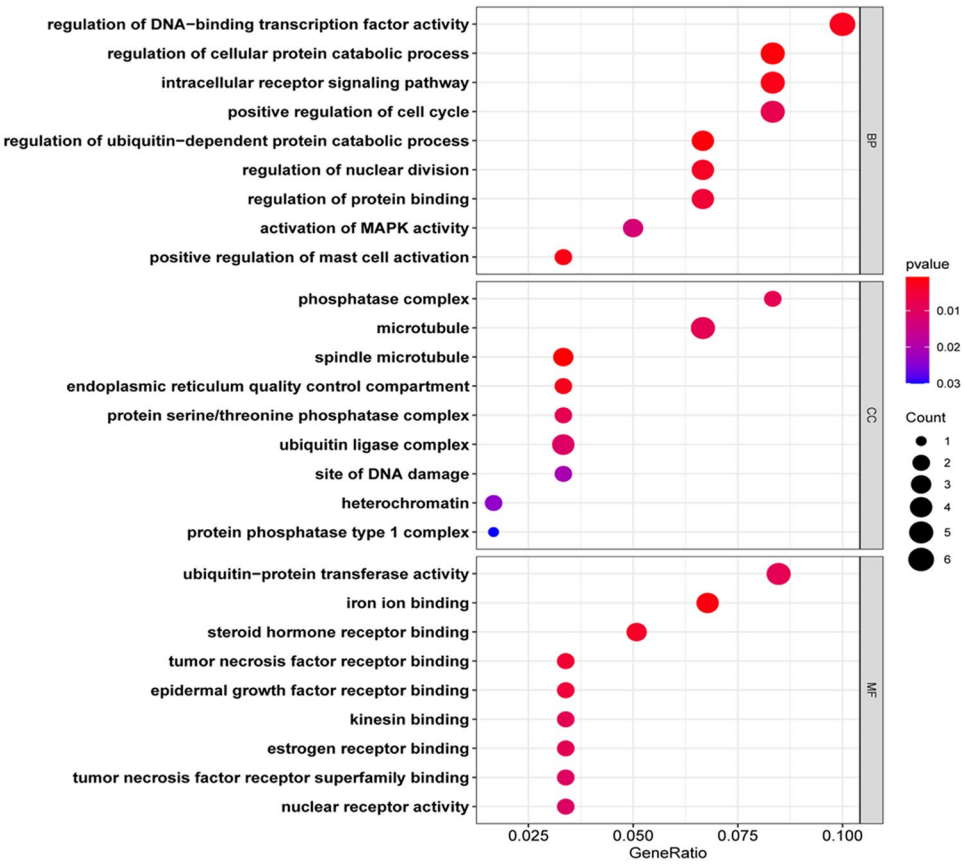

Fig. 3 GO analysis of DEmRNAs in the ceRNA network. Bubble plot of BP, CC, and MF. GO, Gene Ontology; DEmRNAs, differentially expressed messenger RNAs; ceRNA, competing endogenous RNAs; BP, biological processes; CC, cell component; MF, molecular function

Table 3 Functional enrichment analysis of miRNAs in the ceRNA network

Description*	Count	MiRNAs
Aging	8	hsa-mir-30d, hsa-mir-17, hsa-mir-92a-1, hsa-mir-30a, hsa-mir-30e, hsa-mir-204, hsa-mir-155, hsa-mir-92a-2
Autophagy	2	hsa-mir-30a, hsa-mir-106b
Brain development	6	hsa-mir-20a, hsa-mir-106a, hsa-mir-106b, hsa-mir-17, hsa-mir-10b, hsa-mir-155
Cell cycle	10	hsa-mir-20a, hsa-mir-17, hsa-mir-92a-1, hsa-mir-138–2, hsa-mir-125b-2, hsa-mir-205, hsa-mir-27b, hsa-mir-27a, hsa-mir-155, hsa-mir-92a-2
Cell proliferation	9	hsa-mir-379, hsa-mir-17, hsa-mir-92a-1, hsa-mir-127, hsa-mir-433, hsa-mir-125b-2, hsa-mir-93, hsa-mir-27b, hsa-mir-92a-2
DNA damage repair	3	hsa-mir-101–2, hsa-mir-101–1, hsa-mir-155
Glucose metabolism	3	hsa-mir-20a, hsa-mir-125b-2, hsa-mir-375
Immune response	15	hsa-mir-186, hsa-mir-92a-1, hsa-mir-101–1, hsa-mir-155, hsa-mir-892b, hsa-mir-127, hsa-mir-30a, hsa-mir-27b, hsa-mir-92a-2, hsa-mir-101–2, hsa-mir-125b-2, hsa-mir-93, hsa-mir-20a, hsa-mir-17, hsa-mir-27a
Inflammation	14	hsa-mir-584, hsa-mir-20b, hsa-mir-101–1, hsa-mir-137, hsa-mir-155, hsa-mir-27b, hsa-mir-101–2, hsa-mir-138–2, hsa-mir-125b-2, hsa-mir-205, hsa-mir-93, hsa-mir-20a, hsa-mir-17, hsa-mir-27a
Neuron apoptosis	3	hsa-mir-485, hsa-mir-27b, hsa-mir-27a
Neurotoxicity	5	hsa-mir-1226, hsa-mir-92a-1, hsa-mir-27b, hsa-mir-92a-2, hsa-mir-10b
Oxidative stress	1	hsa-mir-137
Response to hypoxia	5	hsa-mir-137, hsa-mir-433, hsa-mir-485, hsa-mir-155, hsa-mir-138–2

*These functions are associated with Parkinson's disease ($P < 0.05$); *miRNAs* microRNAs, *ceRNA* competing endogenous RNAs

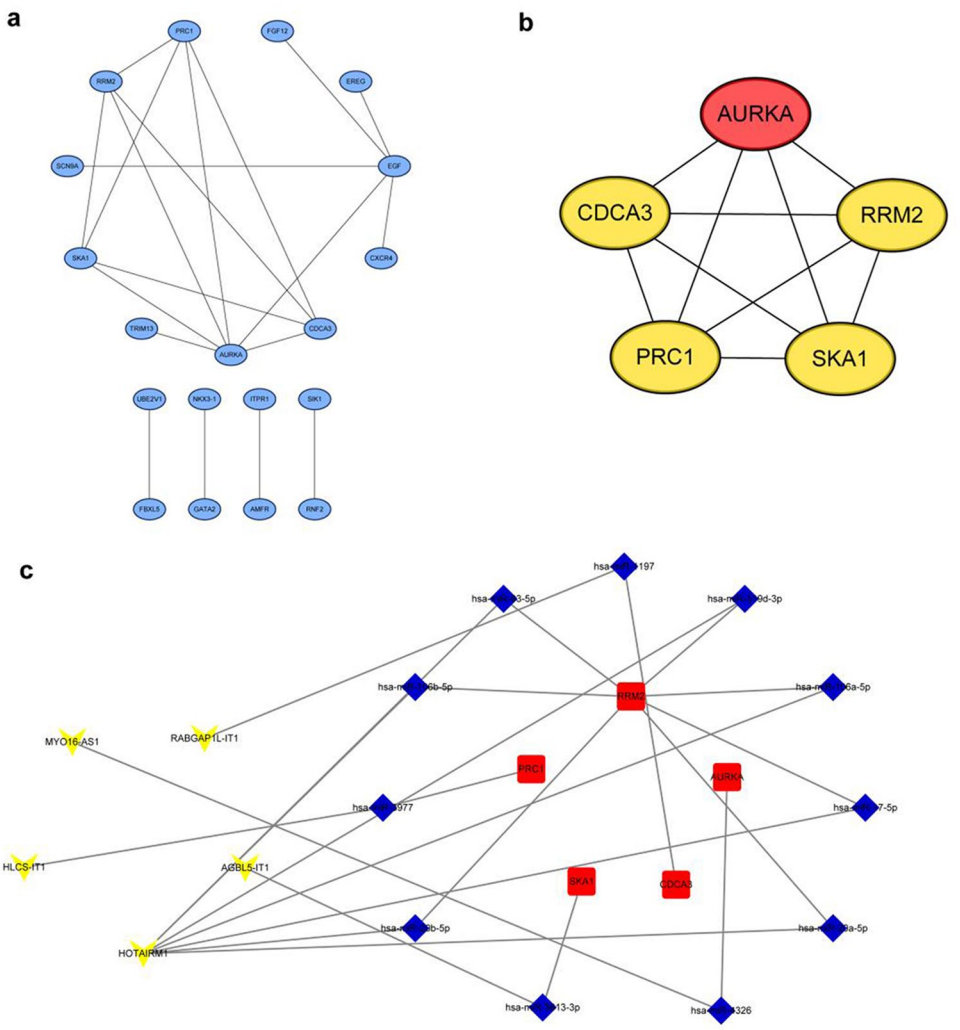

Fig. 4 PPI networks construction, identification of hub genes, and ceRNA subnetwork construction. **a** PPI networks of DEmRNAs in PD. The blue nodes represent proteins. These edges demonstrate the predicted functional associations between the proteins. **b** Five hub genes evaluated by connectivity degree in the PPI network. The change in color from red to yellow represents the connectivity degree from high to low. **c** Construction of the ceRNA subnetwork based on five hub genes. PPI, protein–protein interaction; ceRNA, competing endogenous RNAs; DEmRNAs, differentially expressed messenger RNAs; PD, Parkinson's disease

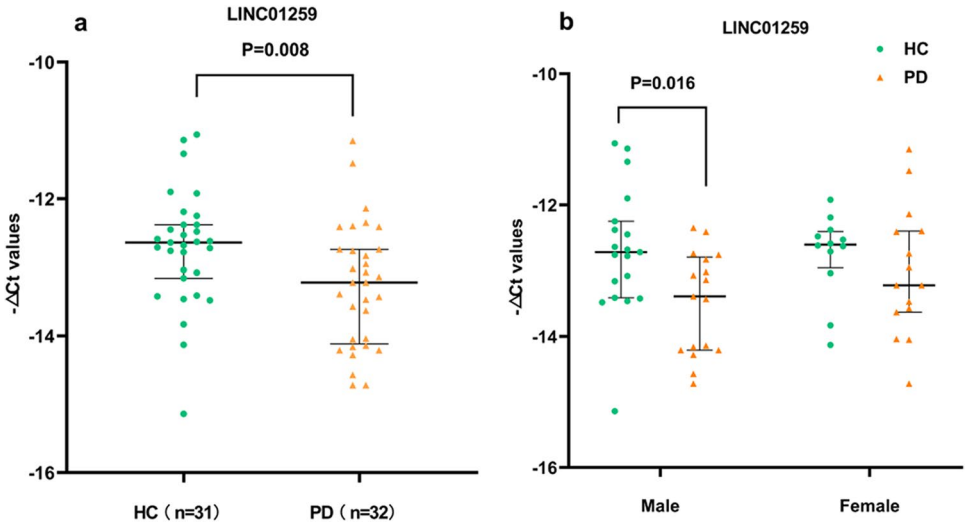

Fig. 5 The expression level of LINC01259 in peripheral blood of 32 PD patients and 31 HC. lncRNA relative expression level was expressed as − ΔCt and relative to the median value for HC (two-tailed Mann–Whitney *U*-test). Horizontal bars indicate median and interquartile range. **a** The expression level of LINC01259 in PD patients was significantly lower than those in HC ($P = 0.008$). **b** The expression level of LINC01259 was significantly different between male patients and male controls ($P = 0.016$). PD, Parkinson's disease; HC, healthy controls

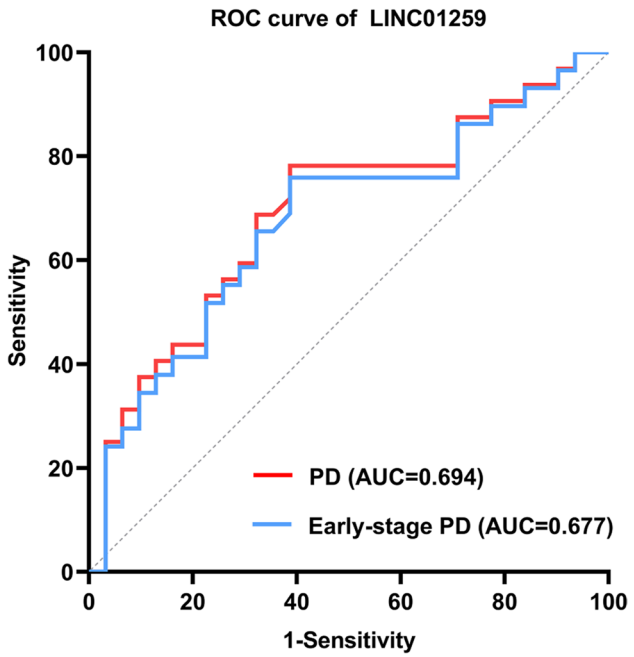

Fig. 6 The diagnostic value of LINC01259 in PD. The red ROC curve of LINC01259 for discriminating PD patients from HC. The AUC was up to 0.694. The blue ROC curve of LINC01259 for discriminating early-stage PD patients from HC. The AUC was up to 0.677. PD, Parkinson's disease; HC, healthy controls; ROC, receiver operating characteristic; AUC, area under the ROC curve

Compared with male controls, LINC01259 expression was lower in male patients ($P = 0.016$), and a similar trend was observed in female cases ($P = 0.373$).

ROC analysis was performed on LINC01259 to further explore whether it could be used as a biomarker for PD and early-stage PD. As shown in Fig. 6, further ROC curve analysis displayed that the diagnostic power of LINC01259 to discriminate PD and early-stage PD was 0.694 and 0.677, respectively. In addition, the area under the ROC curve (AUC), 95% confidence interval (CI), *P*-value, optimal cutoff value, sensitivity, specificity, and Youden index of LINC01259 in differentiating PD and early-stage PD from HC are shown in Table S4. The results indicate that LINC01259 may be a potential biomarker for PD and early-stage PD diagnosis.

Table 4 Pearson correlation of LINC01259 and age, disease duration, disease stage, MDS-UPDRS, MMSE, and MoCA scores in PD patients

Parameters	*R*	*P* value*
Age	−0.24	0.186
Disease duration	0.02	0.904
H-Y stage	−0.03	0.881
MDS-UPDRS III	−0.25	0.161
MDS-UPDRS	−0.21	0.246
MMSE	−0.10	0.576
MoCA	0.20	0.285

*All $P > 0.05$ and $P > 0.05$ are not significant. *H-Y stage* Hoehn-Yahr stage, *MDS-UPDRS III score* Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III score, *MDS-UPDRS total scores* Movement Disorder Society-Unified Parkinson's Disease Rating Scale part total scores, *MMSE* Mini-Mental State Examination, *MOCA* Montreal Cognitive Assessment, *PD* Parkinson's disease

Correlation Between LINC01259 Expression and Disease Severity and Cognitive Ability

Pearson correlation analysis showed no correlation of LINC01259 expression with age of patients, disease duration, disease stage, MDS-UPDRS score, MDS-UPDRS III score, MMSE score and MOCA score, as displayed in Table 4 (all $P > 0.05$).

Potential Biological Functions of LINC01259 on GSEA

GSEA analysis revealed that LINC01259 was significantly enriched in many biological processes relevant to immune response and inflammation, including negative regulation of immune system process, interleukin 1 beta production, positive regulation of myeloid leukocyte differentiation, response to virus, regulation of defense response to virus, interferon gamma production, negative regulation of immune effector process, interleukin 1 production, superoxide metabolic process, and interleukin 8 production (Fig. 7) ($P < 0.05$). The top ten enriched biological processes of LINC01259 are listed in Table S5.

Discussion

Mounting studies have shown that the abnormal expression of lncRNAs is increased in PD patients, indicating their essential role in the pathogenesis of PD [51, 52].

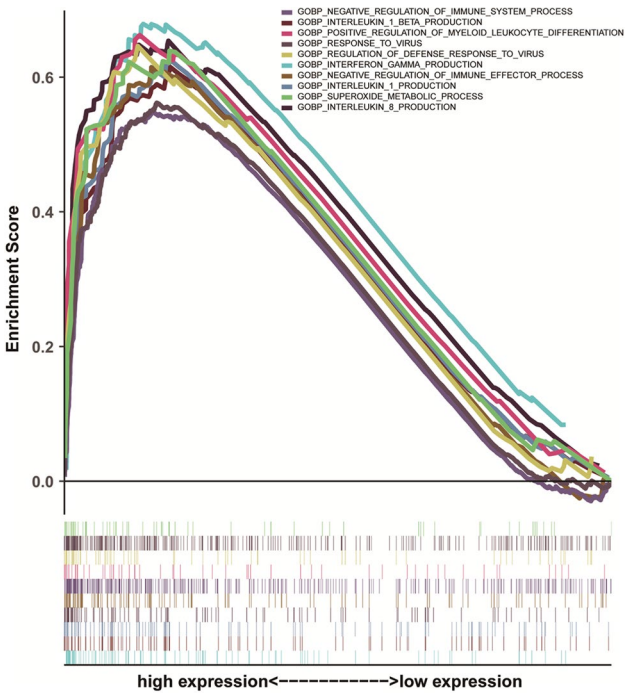

Fig. 7 The ten most enriched biological processes in the GSEA of LINC01259. The ten most significant biological processes of LINC01259 are related to immune response and inflammation. The downregulation of LINC01259 is involved in negative regulation of immune system process, interleukin 1 beta production, positive regulation of myeloid leukocyte differentiation, response to virus, regulation of defense response to virus, interferon gamma production, negative regulation of immune effector process, interleukin 1 production, superoxide metabolic process, and interleukin 8 production. FDR < 0.25 was used to determine the statistical significance of GSEA. GSEA, Gene Set Enrichment Analysis; FDR, false discovery rate

The potential mechanism of lncRNAs in regulating PD progress is under research; many lncRNAs regulate gene expression by acting as miRNA sponges based on the ceRNA hypothesis [53–56]. However, the biological function of numerous lncRNAs in PD remains unknown as yet. In the present study, we used gene expression profiles from the GEO database to construct a PD-specific lncRNA-miRNA-mRNA ceRNA network. Functional enrichment analysis revealed that mRNAs and miRNAs in the ceRNA network were significantly associated with PD-related biological processes. The enrichment results suggested that ceRNA network might regulate the biological processes and pathways of PD. PPI networks were constructed to identify the interactions between the proteins translated by the screened DEGs. Furthermore, a ceRNA subnetwork based on five hub genes (AURKA, CDCA3, PRC1, SKA1, and RRM2) was also set up.

Neuroinflammation is one of the protuberant pathological features of PD. It has been reported that SNHG1 promotes neuroinflammation in the pathogenesis of PD by modulating the miR-7/NLRP3 pathway [57]. By direct interference with miR590-3p, LncZFAS overexpression inhibited the TXNIP/MIB1 E3 ubiquitin ligase/NLRP3 pathway, which regulates the inflammatory signaling pathway of PD [58]. In our study, GO analysis revealed that DEmRNAs are involved in biological processes associated with activation of MAPK activity, which contributes to the pathogenesis of PD, including inflammation and apoptosis [59]. Functional enrichment analysis of miRNAs in the ceRNA network identified underlying functions related to immune response and inflammation. These observations imply that lncRNAs in circulating leukocytes may be involved in PD pathogenesis by regulating the expression of immune response and inflammation-related genes.

LINC01259 (Long Intergenic Non-Protein Coding RNA 1259, HGNC:49,899), also known as TCONS_00007515, belongs to the lncRNA class. It is located on chromosome 14p14 and consists of three exons. In our subsequent investigation of 10 lncRNAs expression in circulating leukocytes, we validated the downregulation of LINC01259 in circulating leukocytes of PD patients for the first time. Due to the fact that our PD patients were recruited mainly from the outpatient clinic with mild symptoms, 29 out of 32 (90.63%) with H-Y stage ≤ 2.5 were at the early stage of PD, and only 3 out of 32 (9.38%) were at the late stage of PD. ROC curve analysis revealed that LINC01259 could be regarded as a potential biomarker for the diagnosis of PD and early-stage PD. Although LINC01259 differed most significantly in circulating leukocytes of PD patients, literature review revealed that the pattern of expression and biological functions of LINC01259 in PD and other diseases have not been established. Our GSEA enrichment analysis

revealed that LINC01259 was remarkably enriched in biological processes associated with negative regulation of immune system process, interleukin 1 beta production, positive regulation of myeloid leukocyte differentiation, response to virus, regulation of defense response to virus, interferon gamma production, negative regulation of immune effector process, interleukin 1 production, superoxide metabolic process, and interleukin 8 production. These findings implied that the downregulation of LINC01259 has a close relationship with immune function and inflammatory response. As is well known, the leukocyte is a key peripheral cell in the development of inflammatory and immune responses. Thus, we speculate that LINC01259 in circulating leukocytes of PD patients is a promising novel molecular connecting immune response and inflammatory processes.

Furthermore, the expression trend of MYO16-AS1 in PD was consistent with the microarray data, and it was close to the limit of significant difference between the two groups ($P=0.167$). Concerning the exploration of HOTAIRM1, our finding is that the upregulation trend of HOTAIRM1 in the ceRNA network is in agreement with the results reported by Fan et al. [32]. However, we did not find significant upregulation of HOTAIRM1 expression in circulating leukocytes of PD patients. The lack of significance might be related to our limited sample size. Thus, further confirmatory studies were demanded in larger sample sizes.

The clinical presentations of PD are diverse. Therefore, we used H&Y stages and MDS-UPDRS to assess motor impairment and MMSE and MoCA to detect cognitive impairment. Our findings suggested that LINC01259 expression was not correlated with age of patients, disease duration, disease stage, MDS-UPDRS score, MDS-UPDRS III score, MMSE score, and MOCA score, which implies its independency from disease severity and cognitive ability in PD patients. Significantly, our finding is that the observed gender-based difference in LINC01259 expression highlighted the moderating role of gender in PD development. For those with PD, the risk of developing PD is twice as high in men as in women. Increasing evidence points to biological sex as an important factor in the development and phenotypical expression of PD [60]. The presence of gender-specific transcription factors and epigenetic regulators might explain such differences between males and females.

Our study has some limitations regarding the small sample size, and validation in larger sample sizes is needed. To further clarify the regulatory mechanism of PD-specific ceRNA network, future studies are needed to validate the expression of miRNAs and DEmRNAs in circulating leukocytes of PD patients. We did not perform in vitro or in vivo studies to unravel the mechanism of LINC01259's involvement in PD pathogenesis, and further experiments are necessary to verify the biological functions of LINC01259 at cellular and animal levels.

In conclusion, the current study provides further evidence for the dysregulation of lncRNAs in peripheral blood leukocytes of PD patients. LINC01259 could be identified as a novel immune and inflammatory biomarker for PD and early-stage PD diagnosis. Evaluation of LINC01259 as a biomarker in larger longitudinal studies is needed to further test its diagnostic utility.

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Data Availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics Approval and Consent to Participate All the participants gave written informed consent. The research on human subjects was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethics committee of the Nanjing First Hospital (ethical permits KY20220124-06).

Consent for Publication All the data is suitable for publication.

Conflict of interest The authors declare no competing interests.

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