bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Association between peripheral inflammation and DATSCAN data of the striatal nuclei in different motor subtypes of Parkinson Disease

Hossein Sanjari Moghaddam [1,+], Farzaneh Ghazi Sherbaf[1,+], Mahtab Mojtahed Zadeh[1], Amir Ashraf-Ganjouei[1], Mohammad Hadi Aarabi [1]

1. *Neurology division, School of medicine, Tehran University of Medical Sciences, Tehran, Iran*

+ Hossein Sanjari Moghaddam and Farzaneh Ghazi Sherbaf have equal contribution.

Corresponding author: Mohammad Hadi Aarabi , Farzaneh Ghazi Sherbaf and Mahtab Mojtahed Zadeh; *School of medicine, Tehran University of Medical Sciences, Poursina St, Keshavarz Blvd, Tehran, Iran*

Email : **Mohammadhadiarabi@gmail.com**, **Farzanghazi@yahoo.com**; **Mahtabmojtahedzadeh@gmail.com**

Tel: +989361853557

Contribution

H.S.M, F.G.S, M.M.Z and M.H.A. contributed to the conception and design of the study; H.S.M, A.A.G and M.H.A. contributed to data collection and analysis; and H.S.M, F.G.S and M.H.A. contributed to writing and revising the manuscript.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Abstract

The interplay between peripheral and central inflammation has a significant role in dopaminergic neural death in nigrostriatal pathway, although no direct assessment of inflammation has been performed in relation to dopaminergic neuronal loss in striatal nuclei. In this study, the correlation of neutrophil to lymphocyte ratio (NLR) as a marker of peripheral inflammation to striatal binding ratios (SBR) of DAT-SPECT images in bilateral caudate and putamen nuclei were calculated in 388 drug-naïve early PD patients (288 tremor-dominant, 73 PIGD, and 27 intermediate) and 148 controls. NLR was significantly higher in PD patients than age and sex-matched healthy controls. NLR showed a negative correlation to SBR in bilateral putamen in all PD subjects. Among our three subgroups, only TD subgroup showed remarkable results. A positive association between NLR and motor severity was observed in TD subgroup. Besides, NLR could negatively predict the SBR in ipsilateral and contralateral putamen and caudate nuclei in tremulous phenotype. Nonetheless, we found no significant association between NLR and other clinical and imaging findings in PIGD and intermediate subgroups, supporting the presence of distinct underlying pathologic mechanisms between tremor and non-tremor predominant PD at early stages of the disease.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Introduction

Progressive dopaminergic demise in the nigrostriatal system has long been considered the pathogenic mainstay of motor features in Parkinson's disease (PD). Lots of ergot mechanisms have been enumerated responsible for the neural loss in PD, of which inflammation, both central and peripheral has been explained in the initiation and progression of PD.

Inflammatory processes, which once were believed to be just the afterclap of neural death, are now considered as an etiological factor, which are also presented in early stages of PD. Several PD susceptibility genes are documented to be involved in the functions of immunity components like microglia (Liu et al., 2011; Pihlstrom et al., 2013; Russo et al., 2014). The result from polymorphism studies determined several pro-inflammatory genes such as IL-1β ,TNF-α, HLA-DBQ1, HLA-DRA, and HLA-DRB1 to be associated with increased susceptibility to PD (Wahner et al., 2007; Ahmed et al., 2012). It is also proved that nonsteroidal anti-inflammatory (NSAIDs) can in long term diminish the risk of PD (Rees et al., 2011). In essence, authors exhibited that dopaminergic neurons are selectively susceptible to oxidative stress and inflammation (Pott Godoy et al., 2008; Liu and Bing, 2011). Freshly, a neuroimaging study using positron emission tomography (PET), detected activated microglia in the SN and putamen of one-year duration PD patients (Iannaccone et al., 2013), implying that there is an active inflammatory condition in initial phases of PD. Furthermore, authors suggested that inflammatory circumstances, both central and peripheral, are present in the prodromal PD (Su and Federoff, 2014; Dzamko et al., 2015). Altogether, these immense lines of evidence highly signify the importance of inflammation in the pathophysiology of PD.

A robust body of evidence has espoused the involvement of peripheral inflammatory conditions in the pathophysiology of PD. In this context, markers of peripheral inflammatory processes including, but not limited to, TNF-α and its receptors and IL-1β have been exhibited to be elevated in in individuals with PD in the peripheral blood (Dobbs et al., 1999; Katsarou et al., 2007; Scalzo et al., 2009; Koziorowski et al., 2012; Rocha et al., 2014), cerebrospinal fluid and post-mortem brain tissues (Mogi et al., 1994; Dobbs et al., 1999; Reale et al., 2009a; Reale et al., 2009b). Related data showed IL-6 is associated with increased risk of development of PD (Scalzo et al., 2010). Besides the peripheral

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

immune markers, peripheral immune cells undergo some quantitative alternations in PD patients. The most prominent of these changes is the lower total number of lymphocytes in individuals with PD compared to controls mainly due to decrement in percentage of CD3+ and CD19+ lymphocytes (Bas et al., 2001; Baba et al., 2005; Saunders et al., 2012; Stevens et al., 2012). Furthermore, decreased counts of T helper cells and increased/unchanged counts of cytotoxic T cells have been documented in PD patients (Calopa et al., 2010).

Owing to the presence of blood-brain-barrier (BBB), central nervous system (CNS) is an immune-privileged organ. However, BBB dysfunction have been postulated to play a key role in the pathogenesis of neurodegenerative diseases like PD (Kortekaas et al., 2005; Hirsch and Hunot, 2009). It has been shown that endothelium residing in SNpc of patients with PD, undergoes radical pathologic morphological changes (Faucheux et al., 1999; Guan et al., 2013), and CD4+ and CD8+ T-lymphocytes have been reported to enter and invade the SNpc of idiopathic PD patients (Phani et al., 2012). Using a mouse model involving injection of vascular endothelial growth factor (VEGF) (a detrimental protein to BBB) into the mice SNpc, researchers demonstrated a significant association between BBB dysfunction and dopaminergic cell death (Rite et al., 2007; Yasuda et al., 2007). , Furthermore, inflammatory cytokines can induce the activation of microglia and therefore the dopaminergic cell death. In this context, one of the valid indicators for peripheral inflammatory processes is the neutrophil to lymphocyte ratio (NLR) (Alkhouri et al., 2012) representing the active inflammation (neutrophils) merged with immunological regulatory processes (lymphocytes).

Despite lots of evidence on the role of inflammation in dopaminergic neural loss, no direct assessment has been performed in this regard. This work was designed to investigate peripheral inflammation in terms of NLR concerning loss of dopaminergic uptake in caudate and putamen on Dopamine Transporter Single Photon Emission Computed Tomography (DaTscan) images, which signifies the dopaminergic activity, among treatment-naïve early PD patients with different motor phenotypes and severities.

2. Methods

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

2.1. Participants

PD patients and healthy control (HC) subjects enrolled in this study were recruited from the Parkinson Progression Markers Initiative (PPMI, http://www.ppmi-info.org/). The study was approved by the institutional review board of all participating sites. Written informed consent was obtained from all participants before study enrolment. The study was performed in accordance with relevant guidelines and regulations. Only baseline visit data are analyzed in this research. PD status was confirmed by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and dopamine transporter deficit was observed on DAT scans. All PD patients at baseline were drug naïve, non-demented, on Hoehn and Yahr (H&Y) staging I or II, and were confirmed negative for any medical or psychiatric disorders apart from PD.

2.2. Clinical assessment and motor classification

Motor and non-motor symptoms were evaluated among subjects with clinical tests at baseline visits at each participating site. The most common PD rating scales, i.e., UPDRS, H&Y staging, and the Schwab and England rating of activities of daily living (Modified Schwab & England ADL) were assessed (Perlmutter, 2009). Tremor score and postural instability and gait difficulty (PIGD) score were identified for PD subjects with MDS-UPDRS. Then PD subjects were classified into 3 groups of tremor dominant (TD), PIGD and intermediate based on the ratio of tremor score/PIGD score. If ratio >= 1.15 or PIGD=0 and tremor>0, then the subject was TD. If ratio <= 0.9, the subject was classified as PIGD. If ratio > 0.9 and < 1.15, or tremor score and PIGD score = 0, the subject was tagged as indeterminate (Stebbins et al., 2013). Non-motor symptoms were investigated by the Montreal Clinic Assessment (MoCA) for mild cognitive impairment, 15-item geriatric depression scale (GDS) for depressive symptoms, The University of Pennsylvania Smell Identification Test (UPSIT) for olfaction function, and independent validation of the scales for outcomes in Parkinson's disease-autonomic (SCOPA-AUT) for autonomic dysfunction.

2.3. Blood sample collection

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

As it is pronounced in the PPMI biologics manual (http://www.ppmi-info.org/), baseline blood sample collection was completed at each study site. PAXgene blood RNA tubes were utilized for the collection of blood samples following the study protocol. The number of neutrophils and lymphocytes were calculated by autoanalyzer device on participants' whole blood samples, right after the collection. NLR was simply calculated by dividing neutrophil to lymphocyte count.

2.4. Dopaminergic imaging

As a preventive measure, all females with the potential of pregnancy were confirmed negative for urine pregnancy test prior to receiving the ^{123}Ioflupane single-photon emission computed tomography (SPECT) injection. None of the subjects had received any of the drugs that would interfere with DAT SPECT imaging within 6 months of screening (full PPMI study protocol is provided at http://www.ppmi-info.org/study-design/research-documents-and-sops/). DAT imaging at baseline visit from all participating cites were centrally reconstructed and were attenuation corrected, followed by spatial normalization for consistent orientation by experienced nuclear medicine experts. Standard volume of interest template was applied on caudate, putamen and occipital regions. Striatal Binding Ratios (SBR) for left and right putamen and caudate were finally calculated, using the formula: (SBR) = (striatal region)/(occipital) -1, where occipital lobe DAT count is the reference (Seibyl et al., 2013). Regarding motor dominancy, SBRs of ipsilateral and contralateral putamen and caudate were compared between PD and HC and within PD motor subtypes. The calculated average of SBRs for the left and the right nuclei is presented for healthy controls or symmetrical motor involvement in PD individuals.

2.5. Statistical analysis

The statistical analysis was performed using SPSS version 22 (BM Corp., Armonk, NY, USA). Pearson's chi-square was used to assess nominal variables across groups. Mann-Whitney U test was used to assess differences between healthy controls and PD patients, and Kruskal-Wallis test was used for multiple comparisons in three groups of PD motor subtypes. Spearman's rank-order correlation

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

was used to test the association between NLR and other characteristics in patients with Parkinson's disease. Finally, *P* values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Between group comparisons

NLR and DAT scan data were provided for 388 de-novo PD patients and 148 HC on baseline visits. Baseline clinical characteristics and detailed demographic data of PD and HC subjects are demonstrated in table 1. Healthy participants were age and sex matched to PD patients, while scored higher on all motor and non-motor tests. As expected, PD patients had significantly lower SBRs in striatal nuclei. NLR was significantly higher in PD cohort.

As shown in table 2, there was no difference between age, gender, UPDRS-III as well as NLR and SBRs in both ipsilateral and contralateral striatal nuclei among PD motor subtypes.

3.2. Correlations between NLR and other clinical and imaging metrics

Spearman's rank-order correlation was performed in healthy controls and three subgroups of PD patients (Table 3). NLR had a strong positive correlation with age and UPDRS III score and a negative correlation with Modified Schwab & England ADL score only in TD subgroup of PD patients. Moreover, TD patients showed negative correlation between NLR values and SBR in contralateral putamen (p-value 0.041) and ipsilateral putamen and caudate regarding motor dominancy (P-values <0.001 and 0.005 respectively). No significant correlation was observed between NLR and other features in two other motor phenotypes. Results did not differ after controlling for the effect of age (data not shown).

Eventually, TD patients were tested for possible correlations between NLR and other characteristics, based on their H&Y stage. In 164 TD Parkinson's disease patients at H&Y stage II, NLR had a positive correlation with age. As TD-patients in H&Y stage II were significantly older than TD patients in stage I (table 4), we carried partial correlation between NLR and SBR in putamen and caudate nuclei, controlling for age. Lower SBRs in bilateral putamen and caudate nuclei were

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

significantly associated with higher NLRs in only the subgroup in stage II (table 5). No significant correlation was found in 124 TD patients with H&Y stage I.

4. Discussion

In search of possible correlation between peripheral inflammation and striatal DAT availability in a large sample of drug-naïve early PD patients, we found that (1) NLR is significantly higher in PD patients than age and sex matched healthy controls. (2) Although NLR and striatal SBR did not differ between subtypes of PD in the early stages of the disease, only TD phenotype and more specifically at H&Y stage II confirmed predictive value of NLR to dopaminergic loss in bilateral striatal nuclei. (3) Worse motor severity was associated with higher NLR values in only TD phenotype.

Tremor is a cardinal motor feature of PD that has always exhibited unalike clinical course to other motor phenotypes. In contrast to TD, non-tremor dominant subtypes, especially PIGD predict worse and rapid disease progression with higher rates of non-motor features such as cognitive decline, mood disturbances, REM sleep behavior disorder and olfaction dysfunction (Jankovic and Kapadia, 2001; Burn et al., 2006; Kumru et al., 2007; Reijnders et al., 2009; Iijima et al., 2011; Konno et al., 2018). A longitudinal study has revealed that TD patients will not develop dementia until irreversibly convert to PIGD phenotype (Alves et al., 2006). Differed clinical pattern is also reflected on structural and functional assays. Autopsy of TD-PD patients has exposed less severe dopaminergic loss in SN than other PD subtypes (Paulus and Jellinger, 1991; Selikhova et al., 2013). This is in concordance with slower progression of symptoms in this group (Jankovic and Kapadia, 2001; Rajput et al., 2009), and is replicated on a recent probabilistic tractography study, which has revealed normal structural connectivity in nigro-pallidal and fronto-striatal circuits in TD patients, which was altered in non-TD (Barbagallo et al., 2017). Postmortem studies have also demonstrated distinct striatal pathology among different PD motor subtypes. While akinesia and rigidity evolve from cell loss in ventrolateral SNpc which project to the posterior putamen, degeneration in TD is most prominent in dorsomedial SNpc projecting to the caudate and anterior putamen, and to the retrorubral field with subsequent

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

projections to the dorsolateral striatum and ventromedial thalamus (Jellinger, 1999). In support of this model, Eggers et al. showed lesions in caudate and lateral putamen (eagle-wing shape) on DATscans of TD patients, compared to lesions in dorsal putamen with egg-shape pattern of dopaminergic loss in akinetic-rigid phenotype (Eggers et al., 2011). This pattern is consistent with our finding of NLR correlation to lower dopamine uptake in both putamen and caudate in TD subgroup, while it was linked to lower DAT binding in putamen and not caudate in all PD patients. In fact, there is consistent report of higher extent of dopamine depletion in putamen than caudate in PD (Pikstra et al., 2016). Moreover, it is proposed that tremor severity may have a different mechanism than other motor features, as in contrast to bradykinesia and rigidity does not depend on the degree of reduced striatal dopamine uptake (Otsuka et al., 1996; Rossi et al., 2010; Eggers et al., 2012; Pikstra et al., 2016), but rather on relative contribution of reduced dopamine in putamen and caudate, indicative of more severe caudate involvement (Otsuka et al., 1996). Therefore, strong correlation of NLR to SBR in caudate of TD patients, but weak association with putamen agrees with these sightings. In this study, we did not find any difference between SBR values in ipsilateral or contralateral caudate and putamen nuclei between three examined subtypes with similar motor stage and severity. However, early drug-naïve TD patients of another study have shown higher DAT availability on bilateral putamen but no difference on caudate nuclei compared to akinetic-rigid PD patients with higher UPDRS-III and H&Y (Moccia et al., 2014). This may point to the possibly greater impact of putamen on motor severity in non-TD phenotype. In this study we did not investigate other neurotransmitters than dopamine which are conferred regarding tremorgenesis and its severity is shown to be mediated by reductions of serotonin transporter availability in the raphe nuclei more than that of dopamine in putamen (Qamhawi et al., 2015; Pasquini et al., 2018), or mediated by neurotransmitter imbalance between reduced GABAergic inhibitory influx from putamen confronted to intact dopaminergic input from SN to the internal pallidum (Rajput et al., 2008).

On the other hand, we found surprisingly, much more substantial reduction in DAT availability in ipsilateral putamen and caudate and a weak reduction in contralateral nuclei in TD patients at H&Y stage II compared to TD at stage I. This is also true for the strong correlation of NLR to ipsilateral

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

caudate (p value= 0.003) and a weak relationship with contralateral caudate nucleus (p value= 0.04). Motor symptoms in PD are considered to evolve from dopaminergic depletion in contralateral nigrostriatal system. However, there are several recent reports of motor dominancy ipsilateral to the side of predominant dopaminergic deficit, especially in TD patients (Aguirregomozcorta et al., 2013; Erro et al., 2013; Hoshiyama et al., 2015). This is also true for medication naïve TD patients from PPMI cohort on early stages of the disease (Kaasinen, 2016). Another study on PPMI cohort (Pasquini et al., 2018) disclosed that a proportion of TD group at baseline progressed to bilateral limb involvement over 2 years follow up, which may be due to the observed ipsilateral striatal dopamine depletion in this study. It is of particular note that TD patients showed negative association between NLR and ipsilateral caudate, while splitting them based on H&Y stage, contralateral caudate emerged to have such association only in the group at stage II. More studies are needed to further elucidate the contribution of ipsilateral basal ganglia motor circuits to the tremorgenesis.

Outside the nigrostriatal tract, imaging studies have imposed the increased functional and metabolic activity of cerebellothalamocortical pathway in emerging parkinsonian tremor, which largely drives by depleted dopaminergic input from basal ganglia (Antonini et al., 1998; Helmich et al., 2011; Lewis et al., 2011). In a recent diffusion tensor imaging study, Wen et al. have revealed that drug-naïve early TD patients recruited from PPMI project have greater white matter integrity and lesser neural degeneration, while they observed widespread white matter dehiscence in PIGD group with similar motor stage and severity. The authors have discussed this finding as a neural compensation for nigrostriatal dopaminergic loss leading to more benign disease course in TD subtype. Additionally, White matter alterations were also more significantly related to severity of symptoms in PIGD than that of TD (Wen et al., 2018).

Overall, different pattern of clinical course and dopaminergic loss along with the consistent findings of involvement of distinct neural circuits outside the nigrostriatal region, strongly suggest the different underlying pathophysiology of PD tremor from that of other motor features (Thenganatt and Jankovic, 2014). This study is the first that has captured the different pathogenesis of the dopaminergic neuronal loss in terms of higher NLR interrelated to lower striatal dopamine in TD but not in non-TD

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Parkinson's disease. NLR is an easy accessible marker of peripheral inflammation that is identified as a predictor of worse outcome in multiple chronic clinical and neurological disorders more prevalent in geriatric population, which also positively correlates to age in normal population (Li et al., 2015). Only two previous studies have investigated the association of NLR in idiopathic PD with opposite results. Akil et al. have found higher NLR in 51 PD (NLR= 3.1 ± 1.3) compared to 50 HC (NLR= 2.1 ± 10.3) (Akil et al., 2015), while Uçar et al. did not find any difference comparing 46 PD (NLR= 2.66 ± 1.05) and 60 HC (NLR= 2.46 ± 1.04) (Uçar et al., 2017). The later study also did not find any difference between TD and akinetic-rigid subtypes. These studies have assessed relatively small sample sizes of PD patients already on dopaminergic replacement therapy, which is shown to recover changes on T-lymphocytes (Kustrimovic et al., 2016). In this study we surveyed larger sample of 388 drug-naïve PD patients who showed higher levels of NLR (2.5 ± 0.9) compared to 148 age-matched healthy controls (NLR= 2.2 ± 0.8), although there was no such difference within PD subtypes. NLR is also shown to be attributed to lower connectivity in several white matter tracts implicated in early or prodromal PD pathology (Haghshomar et al., 2017).

Several studies have manifested that PD progression does not follow a linear model and decline in striatal uptake observed on DATscans are more rapid in early stages of the disease followed by a much more slower progression in advanced stages (Fearnley and Lees, 1991; Jennings et al., 2001; Nurmi et al., 2001). Therefore, it seems that early stages of the disease without the interference of dopaminergic replacement therapy, is the best point during the disease course to evaluate the contribution of inflammation to dopaminergic loss. A growing body of evidence suggests that presynaptic terminals in dorsal striatum undergo degeneration even prior to the SN and axonal degeneration should be the primary target for neuroprotective therapies (Tagliaferro and Burke, 2016). This is supported by in vivo DAT SPECT (Caminiti et al., 2017) and confirms that lower SBRs in putamen and caudate nuclei truly reflect the nigrostriatal pathology in early stages of PD. However, study on early stages impose some limitations that should be considered when interpreting our results. First, motor classification tends to change during the course of the disease, and our subtype classification was only based on screening visits. Second, tremor predominant PD patients recognize

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

the symptoms and seek medical advice earlier and owing to the more benign course more readily cooperate with PPMI project that includes patients not receiving any parkinsonian treatment for 6 months. Therefore, higher number of cases tagged in TD subgroup and relatively fewer cases in PIGD and intermediate in PPMI cohort may have contributed to the false negative results in non-tremor predominant groups. More studies are clearly needed to investigate the generatability of these solid findings.

Conclusion

In this research we investigated the association between immune and nervous system. PD patients were divided into three groups based on tremor/PIGD score, being TD, PIGD, and intermediate subgroups. We demonstrated that NLR can negatively predict SBR in bilateral putamen and caudate nuclei of TD group, and more specifically in stage 2 (H&Y) TD patients. Not observing such association in non-tremor predominant PD patients points to the different pathophysiology mechanisms between tremor and other motor symptoms in PD. Making a bridge between inflammation and neurodegeneration, it is suggested that peripheral inflammation can potentially contribute to the initiation and progression of PD, particularly the process of dopaminergic depletion in striatal regions. However, this relation between peripheral inflammation and parkinson progression is not conclusive. Much more studies are required to further investigate this subject.

Funding: No funding was received for this research.

Financial Disclosure/Conflict of Interest: Authors declare no conflict of interest.

Ethical approval: All procedures performed here, including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Consent for publication

All authors consent for the publication of this study.

Availability of data and materials

All relevant data are available in the Parkinson's Progression Markers initiative (PPMI) database (http://www.ppmi-info.org/data).

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Acknowledgements

Parkinsons Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data) was our primary source of data in this research. For up-to-date information on the study, see www.ppmi-info.org. we gratefully thank all sponsors and funders of PPMI including the Michael J Fox Foundation for Parkinsons Research, AbbVie, Avid Radiopharmaceuticals, Biogen, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GlaxoSmithKline (GSK), Eli Lilly and Company, Lundbeck, Merck, Meso Scale Discovery (MSD), Pfizer, Piramal Imaging, Roche, Servier, and UCB (www.ppmi-info.org/fundingpartners).

References

Aguirregomozcorta, M., Stamelou, M., Antonini, A., Schwingenschuh, P., Prvulovich, L., Edwards, M.J., et al. (2013). Patients with rest-tremor and scans with ipsilateral dopaminergic deficit. *Journal of neurology* 260(4), 1132-1135.

Ahmed, I., Tamouza, R., Delord, M., Krishnamoorthy, R., Tzourio, C., Mulot, C., et al. (2012). Association between Parkinson's disease and the HLA-DRB1 locus. *Mov Disord* 27(9), 1104-1110. doi: 10.1002/mds.25035.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Akil, E., Bulut, A., Kaplan, I., Özdemir, H.H., Arslan, D., and Aluçlu, M.U. (2015). The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. *Neurological Sciences* 36(3), 423.

Alkhouri, N., Morris-Stiff, G., Campbell, C., Lopez, R., Tamimi, T.A., Yerian, L., et al. (2012). Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int* 32(2), 297-302. doi: 10.1111/j.1478-3231.2011.02639.x.

Alves, G., Larsen, J.P., Emre, M., Wentzel-Larsen, T., and Aarsland, D. (2006). Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Movement Disorders* 21(8), 1123-1130.

Antonini, A., Moeller, J.R., Nakamura, T., Spetsieris, P., Dhawan, V., and Eidelberg, D. (1998). The metabolic anatomy of tremor in Parkinson's disease. *Neurology* 51(3), 803-810.

Baba, Y., Kuroiwa, A., Uitti, R.J., Wszolek, Z.K., and Yamada, T. (2005). Alterations of T-lymphocyte populations in Parkinson disease. *Parkinsonism Relat Disord* 11(8), 493-498. doi: 10.1016/j.parkreldis.2005.07.005.

Barbagallo, G., Caligiuri, M.E., Arabia, G., Cherubini, A., Lupo, A., Nisticò, R., et al. (2017). Structural connectivity differences in motor network between tremor-dominant and nontremor Parkinson's disease. *Human brain mapping* 38(9), 4716-4729.

Bas, J., Calopa, M., Mestre, M., Mollevi, D.G., Cutillas, B., Ambrosio, S., et al. (2001). Lymphocyte populations in Parkinson's disease and in rat models of parkinsonism. *J Neuroimmunol* 113(1), 146-152.

Burn, D., Rowan, E., Allan, L., Molloy, S., O'brien, J., and McKeith, I. (2006). Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery & Psychiatry* 77(5), 585-589.

Calopa, M., Bas, J., Callen, A., and Mestre, M. (2010). Apoptosis of peripheral blood lymphocytes in Parkinson patients. *Neurobiol Dis* 38(1), 1-7. doi: 10.1016/j.nbd.2009.12.017.

Caminiti, S.P., Presotto, L., Baroncini, D., Garibotto, V., Moresco, R.M., Gianolli, L., et al. (2017). Axonal damage and loss of connectivity in nigrostriatal and mesolimbic dopamine pathways in early Parkinson's disease. *NeuroImage: Clinical* 14, 734-740.

Dobbs, R.J., Charlett, A., Purkiss, A.G., Dobbs, S.M., Weller, C., and Peterson, D.W. (1999). Association of circulating TNF-alpha and IL-6 with ageing and parkinsonism. *Acta Neurol Scand* 100(1), 34-41.

Dzamko, N., Geczy, C.L., and Halliday, G.M. (2015). Inflammation is genetically implicated in Parkinson's disease. *Neuroscience* 302, 89-102. doi: 10.1016/j.neuroscience.2014.10.028.

Eggers, C., Kahraman, D., Fink, G.R., Schmidt, M., and Timmermann, L. (2011). Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of FP-CIT Single photon emission computed tomography. *Movement Disorders* 26(3), 416-423.

Eggers, C., Pedrosa, D.J., Kahraman, D., Maier, F., Lewis, C.J., Fink, G.R., et al. (2012). Parkinson subtypes progress differently in clinical course and imaging pattern. *PloS one* 7(10), e46813.

Erro, R., Barone, P., Vicidomini, C., Picillo, M., and Pappata, S. (2013). Patients with Parkinson's disease and scans with (predominant) ipsilateral dopaminergic deficit. *Journal of neurology* 260(9), 2405.

Faucheux, B.A., Bonnet, A.M., Agid, Y., and Hirsch, E.C. (1999). Blood vessels change in the mesencephalon of patients with Parkinson's disease. *Lancet* 353(9157), 981-982. doi: 10.1016/s0140-6736(99)00641-8.

Fearnley, J.M., and Lees, A.J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 114(5), 2283-2301.

Guan, J., Pavlovic, D., Dalkie, N., Waldvogel, H.J., O'Carroll, S.J., Green, C.R., et al. (2013). Vascular degeneration in Parkinson's disease. *Brain Pathol* 23(2), 154-164. doi: 10.1111/j.1750-3639.2012.00628.x.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Haghshomar, M., Rahmani, F., Aarabi, M.H., Shahjouei, S., Sobhani, S., and Rahmani, M. (2017). White Matter Changes Correlates of Peripheral Neuroinflammation in Patients with Parkinson's Disease. *Neuroscience*.

Helmich, R.C., Janssen, M.J., Oyen, W.J., Bloem, B.R., and Toni, I. (2011). Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Annals of neurology* 69(2)**,** 269-281.

Hirsch, E.C., and Hunot, S. (2009). Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 8(4)**,** 382-397. doi: 10.1016/s1474-4422(09)70062-6.

Hoshiyama, E., Kadowaki, T., Nakamura, A., Suzuki, K., Hashimoto, K., and Hirata, K. (2015). The decreasing of dopamine-transporter uptake on the right ipsilateral side of tremor in a patient with Parkinson's disease. *Movement Disorders* 30**,** S382.

Iannaccone, S., Cerami, C., Alessio, M., Garibotto, V., Panzacchi, A., Olivieri, S., et al. (2013). In vivo microglia activation in very early dementia with Lewy bodies, comparison with Parkinson's disease. *Parkinsonism Relat Disord* 19(1)**,** 47-52. doi: 10.1016/j.parkreldis.2012.07.002.

Iijima, M., Kobayakawa, T., Saito, S., Osawa, M., Tsutsumi, Y., Hashimoto, S., et al. (2011). Differences in odor identification among clinical subtypes of Parkinson's disease. *European journal of neurology* 18(3)**,** 425-429.

Jankovic, J., and Kapadia, A.S. (2001). Functional decline in Parkinson disease. *Archives of neurology* 58(10)**,** 1611-1615.

Jellinger, K. (1999). "Post mortem studies in Parkinson's disease—is it possible to detect brain areas for specific symptoms?," in *Diagnosis and Treatment of Parkinson's Disease—State of the Art*. Springer), 1-29.

Jennings, D., Innis, R., Seibyl, J., and Marek, K. (Year). "[123I] beta-CIT and SPECT assessment of progression in early and late Parkinson's disease", in: *Neurology*: LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA), A74-A74.

Kaasinen, V. (2016). Ipsilateral deficits of dopaminergic neurotransmission in Parkinson's disease. *Annals of clinical and translational neurology* 3(1)**,** 21-26.

Katsarou, Z., Bostantjopoulou, S., Hatzizisi, O., Giza, E., Soler-Cardona, A., and Kyriazis, G. (2007). [Immune factors or depression? Fatigue correlates in Parkinson's disease]. *Rev Neurol* 45(12)**,** 725-728.

Konno, T., Deutschländer, A., Heckman, M.G., Ossi, M., Vargas, E.R., Strongosky, A.J., et al. (2018). Comparison of clinical features among Parkinson's disease subtypes: A large retrospective study in a single center. *Journal of the Neurological Sciences*.

Kortekaas, R., Leenders, K.L., van Oostrom, J.C., Vaalburg, W., Bart, J., Willemsen, A.T., et al. (2005). Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. *Ann Neurol* 57(2)**,** 176-179. doi: 10.1002/ana.20369.

Koziorowski, D., Tomasiuk, R., Szlufik, S., and Friedman, A. (2012). Inflammatory cytokines and NT-proCNP in Parkinson's disease patients. *Cytokine* 60(3)**,** 762-766. doi: 10.1016/j.cyto.2012.07.030.

Kumru, H., Santamaria, J., Tolosa, E., and Iranzo, A. (2007). Relation between subtype of Parkinson's disease and REM sleep behavior disorder. *Sleep medicine* 8(7)**,** 779-783.

Kustrimovic, N., Rasini, E., Legnaro, M., Bombelli, R., Aleksic, I., Blandini, F., et al. (2016). Dopaminergic receptors on CD4+ T naive and memory lymphocytes correlate with motor impairment in patients with Parkinson's disease. *Scientific reports* 6**,** 33738.

Lewis, M.M., Du, G., Sen, S., Kawaguchi, A., Truong, Y., Lee, S., et al. (2011). Differential involvement of striato-and cerebello-thalamo-cortical pathways in tremor-and akinetic/rigid-predominant Parkinson's disease. *Neuroscience* 177**,** 230-239.

Li, J., Chen, Q., Luo, X., Hong, J., Pan, K., Lin, X., et al. (2015). Neutrophil-to-Lymphocyte Ratio Positively Correlates to Age in Healthy Population. *Journal of clinical laboratory analysis* 29(6)**,** 437-443.

Liu, M., and Bing, G. (2011). Lipopolysaccharide animal models for Parkinson's disease. *Parkinsons Dis* 2011**,** 327089. doi: 10.4061/2011/327089.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Liu, X., Cheng, R., Verbitsky, M., Kisselev, S., Browne, A., Mejia-Sanatana, H., et al. (2011). Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. *BMC Med Genet* 12**,** 104. doi: 10.1186/1471-2350-12-104.

Moccia, M., Pappatà, S., Picillo, M., Erro, R., Coda, A.R.D., Longo, K., et al. (2014). Dopamine transporter availability in motor subtypes of de novo drug-naïve Parkinson's disease. *Journal of neurology* 261(11)**,** 2112-2118.

Mogi, M., Harada, M., Kondo, T., Riederer, P., Inagaki, H., Minami, M., et al. (1994). Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. *Neurosci Lett* 180(2)**,** 147-150.

Nurmi, E., Ruottinen, H.M., Bergman, J., Haaparanta, M., Solin, O., Sonninen, P., et al. (2001). Rate of progression in Parkinson's disease: A 6-[18F] fluoro-L-dopa PET study. *Movement Disorders* 16(4)**,** 608-615.

Otsuka, M., Ichiya, Y., Kuwabara, Y., Hosokawa, S., Sasaki, M., Yoshida, T., et al. (1996). Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms. *Journal of the neurological sciences* 136(1-2)**,** 169-173.

Pasquini, J., Ceravolo, R., Qamhawi, Z., Lee, J.-Y., Deuschl, G., Brooks, D.J., et al. (2018). Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study. *Brain*.

Paulus, W., and Jellinger, K. (1991). The neuropathologic basis of different clinical subgroups of Parkinson's disease. *Journal of Neuropathology & Experimental Neurology* 50(6)**,** 743-755.

Perlmutter, J.S. (2009). Assessment of Parkinson disease manifestations. *Current protocols in neuroscience***,** 10.11. 11-10.11. 14.

Phani, S., Loike, J.D., and Przedborski, S. (2012). Neurodegeneration and inflammation in Parkinson's disease. *Parkinsonism Relat Disord* 18 Suppl 1**,** S207-209. doi: 10.1016/s1353-8020(11)70064-5.

Pihlstrom, L., Axelsson, G., Bjornara, K.A., Dizdar, N., Fardell, C., Forsgren, L., et al. (2013). Supportive evidence for 11 loci from genome-wide association studies in Parkinson's disease. *Neurobiol Aging* 34(6)**,** 1708.e1707-1713. doi: 10.1016/j.neurobiolaging.2012.10.019.

Pikstra, A.R., van der Hoorn, A., Leenders, K.L., and de Jong, B.M. (2016). Relation of 18-F-Dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease. *NeuroImage: Clinical* 11**,** 68-72.

Pott Godoy, M.C., Tarelli, R., Ferrari, C.C., Sarchi, M.I., and Pitossi, F.J. (2008). Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. *Brain* 131(Pt 7)**,** 1880-1894. doi: 10.1093/brain/awn101.

Qamhawi, Z., Towey, D., Shah, B., Pagano, G., Seibyl, J., Marek, K., et al. (2015). Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. *Brain* 138(10)**,** 2964-2973.

Rajput, A., Sitte, H., Rajput, A., Fenton, M., Pifl, C., and Hornykiewicz, O. (2008). Globus pallidus dopamine and Parkinson motor subtypes Clinical and brain biochemical correlation. *Neurology* 70(16 Part 2)**,** 1403-1410.

Rajput, A., Voll, A., Rajput, M., Robinson, C., and Rajput, A. (2009). Course in Parkinson disease subtypes a 39-year clinicopathologic study. *Neurology* 73(3)**,** 206-212.

Reale, M., Greig, N.H., and Kamal, M.A. (2009a). Peripheral chemo-cytokine profiles in Alzheimer's and Parkinson's diseases. *Mini Rev Med Chem* 9(10)**,** 1229-1241.

Reale, M., Iarlori, C., Thomas, A., Gambi, D., Perfetti, B., Di Nicola, M., et al. (2009b). Peripheral cytokines profile in Parkinson's disease. *Brain Behav Immun* 23(1)**,** 55-63. doi: 10.1016/j.bbi.2008.07.003.

Rees, K., Stowe, R., Patel, S., Ives, N., Breen, K., Clarke, C.E., et al. (2011). Non-steroidal anti-inflammatory drugs as disease-modifying agents for Parkinson's disease: evidence from observational studies. *Cochrane Database Syst Rev* (11)**,** Cd008454. doi: 10.1002/14651858.CD008454.pub2.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Reijnders, J., Ehrt, U., Lousberg, R., Aarsland, D., and Leentjens, A. (2009). The association between motor subtypes and psychopathology in Parkinson's disease. *Parkinsonism & related disorders* 15(5)**,** 379-382.

Rite, I., Machado, A., Cano, J., and Venero, J.L. (2007). Blood-brain barrier disruption induces in vivo degeneration of nigral dopaminergic neurons. *J Neurochem* 101(6)**,** 1567-1582. doi: 10.1111/j.1471-4159.2007.04567.x.

Rocha, N.P., Teixeira, A.L., Scalzo, P.L., Barbosa, I.G., de Sousa, M.S., Morato, I.B., et al. (2014). Plasma levels of soluble tumor necrosis factor receptors are associated with cognitive performance in Parkinson's disease. *Mov Disord* 29(4)**,** 527-531. doi: 10.1002/mds.25752.

Rossi, C., Frosini, D., Volterrani, D., De Feo, P., Unti, E., Nicoletti, V., et al. (2010). Differences in nigro-striatal impairment in clinical variants of early Parkinson's disease: evidence from a FP-CIT SPECT study. *European journal of neurology* 17(4)**,** 626-630.

Russo, I., Bubacco, L., and Greggio, E. (2014). LRRK2 and neuroinflammation: partners in crime in Parkinson's disease? *J Neuroinflammation* 11**,** 52. doi: 10.1186/1742-2094-11-52.

Saunders, J.A., Estes, K.A., Kosloski, L.M., Allen, H.E., Dempsey, K.M., Torres-Russotto, D.R., et al. (2012). CD4+ regulatory and effector/memory T cell subsets profile motor dysfunction in Parkinson's disease. *J Neuroimmune Pharmacol* 7(4)**,** 927-938. doi: 10.1007/s11481-012-9402-z.

Scalzo, P., Kummer, A., Cardoso, F., and Teixeira, A.L. (2009). Increased serum levels of soluble tumor necrosis factor-alpha receptor-1 in patients with Parkinson's disease. *J Neuroimmunol* 216(1-2)**,** 122-125. doi: 10.1016/j.jneuroim.2009.08.001.

Scalzo, P., Kummer, A., Cardoso, F., and Teixeira, A.L. (2010). Serum levels of interleukin-6 are elevated in patients with Parkinson's disease and correlate with physical performance. *Neurosci Lett* 468(1)**,** 56-58. doi: 10.1016/j.neulet.2009.10.062.

Seibyl, J., Jennings, D., Grachev, I., Coffey, C., and Marek, K. (2013). 123-I Ioflupane SPECT measures of Parkinson disease progression in the Parkinson Progression Marker Initiative (PPMI) trial. *Journal of Nuclear Medicine* 54(supplement 2)**,** 190-190.

Selikhova, M., Kempster, P.A., Revesz, T., Holton, J.L., and Lees, A.J. (2013). Neuropathological findings in benign tremulous parkinsonism. *Movement Disorders* 28(2)**,** 145-152.

Stebbins, G.T., Goetz, C.G., Burn, D.J., Jankovic, J., Khoo, T.K., and Tilley, B.C. (2013). How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Movement Disorders* 28(5)**,** 668-670.

Stevens, C.H., Rowe, D., Morel-Kopp, M.C., Orr, C., Russell, T., Ranola, M., et al. (2012). Reduced T helper and B lymphocytes in Parkinson's disease. *J Neuroimmunol* 252(1-2)**,** 95-99. doi: 10.1016/j.jneuroim.2012.07.015.

Su, X., and Federoff, H.J. (2014). Immune responses in Parkinson's disease: interplay between central and peripheral immune systems. *Biomed Res Int* 2014**,** 275178. doi: 10.1155/2014/275178.

Tagliaferro, P., and Burke, R.E. (2016). Retrograde axonal degeneration in Parkinson disease. *Journal of Parkinson's disease* 6(1)**,** 1-15.

Thenganatt, M.A., and Jankovic, J. (2014). Parkinson disease subtypes. *JAMA neurology* 71(4)**,** 499-504.

Uçar, C.A., Çokal, B.G., Artık, H.A.Ü., İnan, L.E., and Yoldaş, T.K. (2017). Comparison of neutrophil–lymphocyte ratio (NLR) in Parkinson's disease subtypes. *Neurological Sciences* 38(2)**,** 287-293.

Wahner, A.D., Sinsheimer, J.S., Bronstein, J.M., and Ritz, B. (2007). Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease. *Arch Neurol* 64(6)**,** 836-840. doi: 10.1001/archneur.64.6.836.

Wen, M.-C., Heng, H.S., Lu, Z., Xu, Z., Chan, L.L., Tan, E.K., et al. (2018). Differential White Matter Regional Alterations in Motor Subtypes of Early Drug-Naive Parkinson's Disease Patients. *Neurorehabilitation and neural repair*, 1545968317753075.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Yasuda, T., Fukuda-Tani, M., Nihira, T., Wada, K., Hattori, N., Mizuno, Y., et al. (2007). Correlation between levels of pigment epithelium-derived factor and vascular endothelial growth factor in the striatum of patients with Parkinson's disease. *Exp Neurol* 206(2)**,** 308-317. doi: 10.1016/j.expneurol.2007.05.012.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Table 1

Demographic information and comparison of clinical outcomes between healthy controls and patients with Parkinson's disease.

Characteristic	HCs (n = 148)	PD (n = 388)	*P* Value
Age, mean (SD) [95% CI], y	61.1 (11.3) [59.3-62.9]	61.7 (9.6) [60.7-62.6]	0.775[a]
Female/male, No. (%male)	49/99 (66.9)	134/254 (65.4)	0.755[b]
Left-handed/right-handed, No. (%right-handed) ×	22/119 (80.4)	33/346 (89.2)	0.029[b]
Education, mean (SD) [95% CI], y	16.1 (3.0) [15.7-16.6]	15.5 (3.0) [15.2-15.8]	0.034[a]
Disease duration, median (range), m	…	4.0 [0-36]	…
NLR, mean (SD) [95% CI]	2.2 (0.8) [2.1-2.3]	2.5 (0.9) [2.4-2.6]	<0.001[a]
SBR score in Caudate nucleus, mean (SD) [95% CI]	3.0 (0.6) [2.9-3.1]	1.8 (0.6) [1.8-1.9]	<0.001[a]
SBR score in Putamen nucleus mean (SD) [95% CI]	2.1 (0.5) [2.0-2.2]	0.7 (0.3) [0.6-0.7]	<0.001[a]
Hoehn and Yahr stage, mean (SD)	…	1.6 (0.5)	…
MDS-UPDRS part I score, mean (SD)	3.0 (2.7)	5.6 (4.0)	<0.001[a]
MDS-UPDRS part II score, mean (SD)	0.4 (1.0)	6.0 (4.2)	<0.001[a]
MDS-UPDRS part III score, mean (SD)	1.2 (2.1)	20.4 (8.8)	<0.001[a]
Modified Schwab & England ADL, mean (SD)	…	93.2 (6.0)	…
MoCA score, mean (SD)	28.2 (1.1)	27.1 (2.3)	<0.001[a]
GDS score, mean (SD)	1.1 (1.5)	2.3 (2.4)	<0.001[a]
UPSIT score, mean (SD)	34.4 (4.5)	22.3 (8.2)	<0.001[a]
SCOPA-AUT score, mean (SD)	5.7 (3.5)	9.4 (6.0)	<0.001[a]

Abbreviations: HCs, healthy controls; PD, Parkinson disease; NLR, Neutrophil to lymphocyte ratio; SBR, Striatal binding ratios; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal cognitive assessment; GDS, Geriatric depression scale; Modified Schwab & England ADL, overall activities of daily living; UPSIT, University of Pennsylvania Smell Identification Test; SCOPA-AUT, Scales for Outcomes in Parkinson's disease.

× Others were mixed-handed

[a]Based on Mann-Whitney *U* test.
[b]Based on χ^2 test.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Table 2

Demographic data and comparison of certain characteristics between patients with Parkinson's disease based on Tremor/PIGD score ratio.

Characteristic		PIGD * (n = 73)	Indeterminate (n = 27)	TD (n = 288)	*P* Value
Age, mean (SD) [95% CI], y		60.8 (9.5) [58.6-63.0]	62.8 (10.0) [58.8-66.8]	61.8 (9.7) [60.7-62.9]	0.744 [a]
Female/male, No. (%male)		29/44 (60.0)	6/21 (77.7)	99/189 (65.6)	0.261 [b]
MDS-UPDRS part III score, mean (SD) [95% CI]		19.2 (8.7) [17.1-21.2]	18.1 (7.7) [15.1-21.2]	20.4 (9.0) [19.9-22.0]	0.195 [a]
NLR, mean (SD) [95% CI]		2.5 (0.8) [2.3-2.6]	2.6 (1.0) [2.2-3.0]	2.5 (1.0) [2.4-2.6]	0.952 [a]
SBR in contralateral^ nuclei, mean (SD) [95% CI]	Caudate	1.8 (0.6) [1.6-1.9]	1.8 (0.5) [1.6-2.0]	1.8 (0.6) [1.8-1.9]	0.631 [a]
	Putamen	0.7 (0.3) [0.6-0.8]	0.6 (0.2) [0.5-0.7]	0.7 (0.3) [0.6-0.7]	0.163 [a]
SBR in ipsilateral nuclei, mean (SD) [95% CI]	Caudate	2.1 (0.7) [2.0-2.3]	2.1 (0.6) [1.9-2.4]	2.2 (0.6) [2.1-2.2]	0.813 [a]
	Putamen	1.0 (0.4) [0.8-1.0]	1.0 (0.4) [0.8-1.2]	1.0 (0.4) [0.9-1.0]	0.713 [a]

Abbreviations: NLR, Neutrophil to lymphocyte ratio; SBR, Striatal binding ratios; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

*The ratio of tremor and PIGD score in MDS-UPDRS. Parkinson's disease patients with a ratio of ≥1.15 were classified as tremor-dominant (TD), ratio ≤0.90 were classified as PIGD and 0.90 < ratio < 1.15 were classified as intermediate.

^Contralateral and ipsilateral striatal nuclei are against the side of motor dominancy.

[a]Based on Kruskal-Wallis test.
[b]Based on χ^2 text.

Table 3

The correlation (Spearman) between NLR and other characteristics in healthy controls and patients with Parkinson's disease based on Tremor/PIGD score ratio.

		Age	Disease duration	Tremor score	PIGD score	UPDRS part III score	Modified Schwab &England ADL	UPSIT score	MoCA score	SCOPA-AUT score	SBR score in Caudate	SBR score in Putamen	SBR score in Caudate (ipsilateral)	SBR score in Putamen (ipsilateral)
NLR, *P* value (rho)	**HCs (n = 148)**	0.405 (0.069)	…	…	…	0.388 (-0.072)	…	0.133 (-0.124)	0.704 (-0.031)	0.480 (-0.059)	0.590 (-0.045)	0.702 (-0.032)	…	…
	All PD (n = 388)	**0.011 (0.129)**	0.495 (0.035)	0.066 (0.093)	0.662 (0.022)	0.058 (0.096)	**0.015 (-0.123)**	0.744 (-0.017)	0.891 (-0.007)	0.185 (0.067)	0.199 (-0.066)	**0.026 (-0.114)**	**0.014 (-0.126)**	**0.002 (-0.158)**
	PIGD * (n = 73)	0.991 (0.001)	0.834 (0.025)	0.706 (-0.045)	0.667 (0.051)	0.947 (-0.008)	0.695 (0.047)	0.732 (-0.041)	0.232 (0.142)	0.581 (0.066)	0.947 (0.008)	0.780 (-0.033)	0.936 (0.010)	0.942 (0.009)
	Indeterminate (n = 27)	0.813 (-0.048)	0.488 (-.139)	0.867 (0.034)	0.921 (0.020)	0.374 (-0.178)	0.058 (-0.370)	0.926 (0.019)	0.524 (0.128)	0.720 (0.072)	0.97 (0.008)	0.287 (-0.213)	0.953 (0.012)	0.659 (-0.089)
	TD (n = 288)	**0.003** (0.172)	0.371 (0.053)	0.050 (0.116)	0.603 (0.031)	**0.009** (0.155)	**0.015** (-0.144)	0.685 (-0.024)	0.426 (-0.047)	0.214 (0.073)	0.106 (-0.096)	**0.041 (-0.120)**	**0.005 (-0.168)**	**<0.001 (-0.208)**

Abbreviations: HCs, healthy controls; PD, Parkinson's disease; PIGD, Postural instability–gait difficulty; NLR, Neutrophil to lymphocyte ratio; UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal cognitive assessment; Modified Schwab & England ADL, overall activities of daily living; UPSIT, University of Pennsylvania Smell Identification Test; SCOPA-AUT, Scales for Outcomes in Parkinson's disease; SBR, Striatal binding ratios.

*The ratio of tremor and PIGD score in MDS-UPDRS. Parkinson's disease patients with a ratio of ≥1.15 were classified as tremor-dominant (TD), ratio ≤0.90 were classified as PIGD and 0.90 < ratio < 1.15 were classified as intermediate.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Table 7

Demographic information and comparison of clinical outcomes in patients with Parkinson's disease based on Hoehn and Yahr stage.

Characteristic	H&Y stage I (n = 124)	H&Y stage II (n = 164)	*P* Value
Age, mean (SD), y	59.0 (9.9)	63.9 (8.9)	<0.001[a]
Disease duration, median (range), m	4.0 [1-35]	4.0 [0-36]	0.864[a]
NLR, mean (SD)	2.4 (0.9)	2.7 (1.0)	0.003[a]
SBR score in Caudate nucleus (contralateral), mean (SD)	1.9 (0.6)	1.8 (0.5)	0.166[a]
SBR score in Putamen nucleus (contralateral), mean (SD)	0.7 (0.3)	0.7 (0.2)	0.032[a]
SBR score in Caudate nucleus (ipsilateral) , mean (SD)	2.3 (0.6)	2.1 (0.5)	0.004[a]
SBR score in Putamen nucleus (ipsilateral) , mean (SD)	1.1 (0.4)	0.9 (0.3)	<0.001[a]
Tremor score, mean (SD)	0.5 (0.2)	0.6 (0.3)	0.017[a]
PIGD score, mean (SD)	0.1 (0.1)	0.2 (0.2)	0.056[a]
MDS-UPDRS part III score, mean (SD)	15.1 (5.4)	25.4 (8.5)	<0.001[a]
Modified Schwab & England ADL, mean (SD)	95.2 (5.1)	92.0 (5.8)	<0.001[a]
MoCA score, mean (SD)	27.3 (2.2)	26.8 (2.4)	0.074[a]
GDS score, mean (SD)	2.1 (2.5)	2.4 (2.3)	0.081[a]
UPSIT score, mean (SD)	23.7 (8.1)	21.0 (8.0)	0.006[a]
SCOPA-AUT score, mean (SD)	9.0 (6.4)	10.3 (6.1)	0.051[a]

Abbreviations: H&Y, Hoehn and Yahr stage; NLR, Neutrophil to lymphocyte ratio; SBR, Striatal binding ratios; PIGD, Postural instability–gait difficulty; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MOCA, Montreal cognitive assessment; GDS, Geriatric depression scale; Modified Schwab & England ADL, Overall activities of daily living; UPSIT, University of Pennsylvania Smell Identification Test; SCOPA-AUT, Scales for Outcomes in Parkinson's disease.

[a]Based on Mann-Whitney *U* test.

Table 4

The correlation (Spearman) between NLR and other characteristics in patients with tremor dominant Parkinson's disease (TD) based on Hoehn and Yahr stage.

											Contralateral* Nuclei		Ipsilateral Nuclei	
		Age	Disease duration	Tremor score	PIGD score	UPDRS part III score	Modified Schwab &England ADL	UPSIT score	MoCA score	SCOPA-AUT score	SBR score in Caudate	SBR score in Putamen	SBR score in Caudate	SBR score in Putamen
NLR, *P* value (rho)	**H&Y stage I (n = 124)**	0.902 (-0.011)	0.548 (-0.055)	0.563 (0.052)	0.242 (-0.106)	0.486 (0.063)	0.064 (-0.167)	0.263 (0.101)	0.754 (0.028)	0.980 (0.002)	0.738 (-0.030)	0.947 (-.006)	0.640 (-0.043)	0.541 (-0.056)
	H&Y stage II (n = 164)	**0.002** (0.240)	0.088 (0.134)	0.140 (0.116)	0.217 (0.097)	0.278 (0.085)	0.352 (-0.073)	0.292 (-0.083)	0.338 (-0.075)	0.241 (0.092)	**0.040 (-0.162)**	**0.017 (-0.188)**	**0.003 (-0.221)**	**0.019 (-0.185)**

Abbreviations: H&Y, Hoehn and Yahr stage; NLR, Neutrophil to lymphocyte ratio; UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal cognitive assessment; Modified Schwab & England ADL, overall activities of daily living; UPSIT, University of Pennsylvania Smell Identification Test; SCOPA-AUT, Scales for Outcomes in Parkinson's disease; SBR, Striatal binding ratios.

*Contralateral and ipsilateral nuclei are against the side of motor dominancy. Numbers for all SBRs are representative of added partial correlation between NLR and SBR in putamen and caudate nuclei, controlling for age.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

bioRxiv preprint doi: https://doi.org/10.1101/247080; this version posted March 10, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.