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Investigation of the relationship between lumbar spine MRI findings and pain in patients who received and did not receive Parkinson's treatment

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ABSTRACT

Objectives: Parkinson's disease is a chronic, progressive neurodegenerative disorder. Pain is a common symptom in Parkinson's disease, but the prevalence, characteristics, and documentation of its relationship with Parkinson's disease are insufficient. In this study, it was aimed to evaluate the relationship between lumbar spine magnetic resonance imaging (MRI) findings in patients who received and did not receive Parkinson's treatment.

Methods: The demographic characteristics of patients with diagnosed Parkinson's disease were retrospectively obtained from the records. Their pain was grouped and the Hoehn Yahr stage at the first examination, and the interventional treatments performed were recorded. MRI measurements were made in the axial plane and sagittal plane of the spinal canal, whereas Ligamentum flavum measurements were made on both the right and left sides.

Results: Twenty-six patients were included in the study. The average age was 73.5. Notably, 57.7% of patients were not diagnosed with Parkinson's disease prior to admission, while the Hoehn Yahr stage mostly comprised Stage 2 with 53.8%. Additionally, low back, waist, and hip pain was observed in 84.6% (n = 22), whereas 61.5% (n = 16) of patients experienced radicular pain. Epidural injections accounted for 33.2%. On lumbar MRI, the most narrow spinal segment on axial measurement was shown to be L4-L5. The axial spinal canal measurement of the Hoehn Yahr 1 group was observed to be significantly lower than the Hoehn Yahr 2 group.

Conclusions: Optimal management for lumbar pain that increases with age is currently inadequate. There is a need to conduct larger studies on pain complaints, which is one of the frequently experienced non-motor symptoms in Parkinson's disease, as well as the interventional methods applied.

Keywords: Pain, Parkinsonism, low back pain, epidural, spinal stenosis

Parkinson's disease (PD) is a chronic, progressive, and neurodegenerative disease. As the disease progresses, motor impairments and non-motor symptoms create significant disease burdens. Therefore, the goal of treatment is to relieve symptoms. Pain is common in patients with Parkinson's disease, but the

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prevalence, characteristics, and documentation of its relationship with Parkinson's disease are insufficient [1].

To the best of our knowledge, different studies have elucidated all kinds of pain with a high frequency of up to 65% or 85% at different rates. In a study evaluating that the pain perceived by patients is directly related to PD, the pain experienced by 46% of patients was attributed to PD. Some studies have investigated specific types of pain or specifically localized pain areas in PD patients. For example, the prevalence of low back pain has been reported to be 60-74% [2-7]. The need for large population-based studies on the review of non-motor symptoms and the prevalence of pain and other non-motor symptoms in PD patients has also been emphasized [2-4].

Pain management may indicate the magnitude of pain as a clinical problem in PD patients. As the disease progresses, musculoskeletal, radicular, and dystonic pain become more frequent. This is probably attributed to pathologically increased muscle tone and the long-term worsening of postural reflexes. Moreover, as these postural disturbances (anteflexion, kyphoscoliosis) progress, the non-radicular back pain gradually turns into radicular pain. Furthermore, central pain is likely to worsen with neurodegeneration spreading to the central sensory pathways [3, 5, 6].

In addition to the deterioration of muscular imbalance limb deformities, degeneration of the neck, trunk, or lumbar region, and axial sagittal or frontal deformities can also cause pain due to the movement disorder itself. The lumbar region has been shown to cause more musculoskeletal pain in PD compared to the control group. Back pain appears to be an early and common symptom in PD. Patients with PD deal with chronic low back pain more than those belonging to the same age group [4, 7-9]. Lumbar spinal canal stenosis (LSCS) is known to be the most common spinal disorder among elderly patients. The narrowing of the canal is partly caused by ligamentum flavum (LF) hypertrophy, which mechanically compresses the nerve root or cauda equina [10].

Joints between vertebrae are strengthened and supported by many ligaments. One of them is LF, which adheres to the front of the upper lamina and to the back of the lower lamina. Due to the connective tissue, it affects the instability of the spine, controls the intervertebral movement, and creates a protective surface for the posterior dural sac. LF hypertrophy is considered an important cause of radiculopathy in lumbar degenerative disease [11-13].

It is argued that altered posture and abnormal muscle tone in Parkinson's patients can increase stress on both lumbar discs, soft tissue, as well as bone structures of the lumbar spine. Truncal dystonia may additionally contribute to focal distress and other related problems. Whether the relationship between PD and low back pain is specific remains unclear as it is common in both cases [7, 14].

This study aims to describe the clinical and demographic predictors of pain, including the types of pain, painful areas, and the diagnosis that cause pain in patients admitted to the pain outpatient clinic with primary pain complaints or before the diagnosis of PD, as well as the use of different interventional pain treatments. This is done to evaluate the relationship between lumbar spinal canal measurement, LF measurements, and PD staging in patients with low back pain.

METHODS

The study was initiated in accordance with the Helsinki declaration and after obtaining the approval of the local ethics committee (Sakarya University Faculty of Medicine ethical committee, number E-71522473-0.50.01.04-15084). Patients who applied to Sakarya Training and Research Hospital Neurology and Pain outpatient clinic between 2019-2021 were diagnosed with Parkinson's or had Parkinson's disease, but were not diagnosed in another center. Patients who were diagnosed by pain specialists and neurologists according to UK PD Brain Bank Criteria [15] were retrospectively removed from the hospital records. A pain physician and neurologist examined the patients.

Inpatient and outpatient records were reviewed, focusing on the presence of pain complaints in the personal history of patients with PD or those who were newly diagnosed. Demographic characteristics, pain that prompted patients to seek medical help, and first-time complaints were noted. In pain classification, especially those with back pain, waist, hip pain is in the Back/Waist/ Hip Pain group; in the radicular pain group, those with radicular pain that spread to the extremity towards the arm or leg; in the joint pain group,

with or without movement disorders, the knee or shoulder area is specified; in the peripheral neuropathic pain group, patients with symptoms of mononeuropathy such as tingling and dysesthesia in the extremities, bilateral distal symmetrical neuropathic pain or entrapment neuropathy and clinical laboratory evidence and also who met diagnostic criteria for neuropathic pain; orofacial pain or neuralgiform pain was collected in the neuralgia/orofacial pain group. Lumbar magnetic resonance imaging (MRI) records were checked, since the treatment of patients and the most common low back pain was observed. Anteroposterior (AP) spinal canal measurement in the sagittal plane in lumbar MRI was measured at three different levels in T2-weighted imaging (T2WI) and the narrowest AP spinal canal measurement in T2WI in the axial section. Multiple measurements made in the sagittal plane were taken at the lumbar vertebra levels comparatively, and at the levels closest to the AP measurement in the axial section, in order to minimize the error caused by postural posture disorders during imaging. LF measurements were done with the help of hospital imaging software. The maximum thickness of the LF was measured on both the right and left sides at the most narrow lumbar levels. The measurement was made in T2WI perpendicular to the lamina, right and left-sided, mid-width distance (Fig. 1).

The types of treatment received by the patients and the Hoehn Yahr (HY) stages at the first examination were also noted. The two most important conditions in the HY staging are whether the disease is bilateral or postural disorder. Therefore, increased parkinsonian motor impairment can encompass unilateral (Stage 1) to bilateral disease (Stage 2), the presence of postural imbalance (Stage 3), the loss of physical independence (Stage 4), and being tied to a wheelchair or bed (Stage 5) [16].

The pain types of patients were classified as acute, duration less than three months, whereas those with a long duration were classified as chronic. For the pain that caused the patient to come to the pain clinic, the diagnosed pain syndrome or its etiological cause, and the interventional procedure for pain were recorded.

Statistical Analysis

The research data were evaluated by being uploaded to the computer environment via ―SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as median (minimum-maximum), frequency distribution, and percentage. The variables' suitability to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Tests). Kruskal-Wallis and Mann-Whitney U Tests were used for groups that did not conform to normal distribution. Statistical significance level was accepted as $p < 0.05$.

RESULTS

Twenty-six patients were included in the study and their data were analyzed. It was observed that the av-

Table 1. Sociodemographic features (n = 26)

Parameter		Data
Age (years)		Median 73.5 (Q1:69-Q3:78)
Gender, n (%)	Male	13 (50)
	Female	13 (50)
Previously diagnosed with PD, n (%)	Yes	15 (57.7)
	No	11 (42.3)
HY stage, n (%)	1	4 (15.4)
	2	14 (53.8)
	3	8 (30.8)

PD = Parkinson disease, HY = Hoehn Yahr

Table 2. Diagnosed pain syndromes

Parameter	n	%
Lumbar radiculopathy + Lumbar spinal stenosis	13	32.5
Lumbar radiculopathy	4	10
Failed back surgery	4	10
Knee osteoarthritis	4	10
Cervical radiculopathy	3	7.5
Lumbar vertebra fracture	2	5
Shoulder impingement syndrome	2	5
Postzoster neuralgia	2	5
Polyneuropathy	2	5
Carpal tunnel syndrome	1	2.5
Trigeminal neuralgia	1	2.5
Sciatica axonal neuropathy	1	2.5
Plexopathy	1	2.5

Table 3. Interventional treatments applied

Interventional treatments	n	%
Genicular block	1	3.3
MILD procedure	1	3.3
Intercostal block	1	3.3
Caudal epidural steroid injection	5	16.6
Lumbar epidural steroid injection	4	13.3
Sacroiliac injection	1	3.3
Mandibular block	1	3.3
Lumbar faset median nerve block	5	16.6
Epiduroscopy	1	3.3
Transforaminal epidural steroid injection	1	3.3
Facet median branch radiofrequency coagulation	2	6.6
Piriformis injection	1	3.3
Spinal cord stimulator implantation	1	3.3
Paravertebral trigger point injection	1	3.3
Vertebroplasty/kyphoplasty	2	6.6
Intraartricular knee injection	1	3.3
Erector spina plane block	1	3.3

MILD = Minimal Invasive Lumbar Decompression

erage age of these patients was 73.5 and that the number of males and females was equal. Notably, 57.7% of patients were not diagnosed with PD before the application, and the HY stage mostly comprised Stage 2 with 53.8%. Moreover, 80.8% were found to have an additional disease. Table 1 illustrates the sociodemographic characteristics of the patients.

The prevalence of comorbid diseases in patients was as follows: 50% hypertension, 38.5% coronary artery disease, 26.9% diabetes mellitus, 11.5% thyroid disease, and 11.5% cancer. Previous joint or lumbar surgery was observed in 42.3% (n = 11) of patients. Similarly, lumbar surgery was seen in 38.5% (n = 10) of patients. The presence of rotoscoliosis was observed in 23.1% (n = 6) of patients.

In terms of pain classification, the following observations were made: 84.6% (n = 22) of patients had low back, waist, and hip pain, 61.5% (n = 16) experienced radicular pain, and 15 of these patients had pain radiating to the radicular lower extremity. Similarly, 38.5% (n = 10) of patients with knee or shoulder joint pain, 23.1% (n = 6) of patients experiencing peripheral neuropathic pain, including distal symmetrical, or mononeuropathy/plexopathy, and 15.4% (n = 4) of patients with neuralgia/orofacial pain were determined. The etiological diagnoses based on these complaints and imaging methods are shown in Table 2. In some patients, more than one diagnosis was made for the painful condition.

It was observed that 57.7% (n = 15) of patients were using drugs for PD. The most common drugs used by the patients were dopamine agonist or MAO-B inhibitor and L-dopa combination therapy. Most of them were already on medical treatment for pain. Interventional pain treatments applied to patients are depicted in Table 3. The frequency percentage within the procedures was given due to the interventional treatments performed on a patient undergoing more than one procedure.

The minimum and maximum values of the patients' lumbar MRI measurements are shown in Table 4, whereas the relationship between the HY phase and Canal measurements is shown in Table 5. In the study, the narrowest lumbar range was found to be 42.3% (n = 11), most frequently at the L4-5 level. We know that the disability of the disease and posture disorders is

Table 4. **Measurements**

Parameter		Median	Q1-Q3
Lumbar MRI sagittal spinal canal measure 1		13.3	(10.4-14.4)
Lumbar MRI sagittal spinal canal measure 2		12.8	(9.9-14.05)
Lumbar MRI sagittal spinal canal measure 3		12.8	(10.0-13.5)
Lumbar MRI sagittal spinal canal measure mean		12.96	(10.53-14.74)
Lumbar MRI axial spinal canal AP measure		12.0	(9.9-15.1)
Lumbar axial lig. flavum measure 1		6	(5.3-6.7)
Lumbar axial lig. flavum measure 2		5.7	(4.8-6.6)
Lumbar axial lig. flavum measure mean		6.05	(5.05-6.6)
Parameter		**n =26**	**%**
Lumbar MRI	L1-L2	2	7.7
The most narrow spinal segment on axial	L2-L3	2	7.7
	L3-L4	7	26.9
	L4-L5	11	42.3
	L5-S1	1	3.8

Measurements are given as mm. MRI = Magnetic Resonance Imaging

Table 5. **HY and measurements**

Parameter	HY1 (n = 4)	HY2 (n = 14)	HY3 (n = 8)	KW	*p* value
Lumbar MRI sagittal spinal canal measure 1	7.55 (4.7-9.45)	13.8 (12.25-14.3)	13.35 (9.72-15.6)	3.481	0.175
Lumbar MRI sagittal spinal canal measure 2	8.15 (6.4-10.23)	13.8 (11.4-14.7)	12.3 (8.65-13.55)	4.927	0.084
Lumbar MRI sagittal spinal canal measure 3	8.95 (7.9-9.2)	12.8 (11.65-13.7)	13.0 (9.05-13.7)	2.537	0.281
Lumbar MRI sagittal spinal canal measure mean	8.21 (6.5-9.34)	13.53 (11.41-14.86)	12.81 (9.39-14.36)	4.134	0.127
Lumbar MRI axial spinal canal AP measure	7.2 (5.1-8.7)	14.0 (11.81-15.6)	10.7 (8.77-12.27)	9.043	**0.011***
Lumbar axial lig. flavum measure 1	6.4 (6.1-6.73)	5.9 (5.1-6.5)	6.05 (5.35-6.57)	1.170	0.557
Lumbar axial lig. flavum measure 2	5.3 (4.0-6.1)	5.6 (4.85-6.55)	6.25 (4.65-6.62)	0.195	0.907
Lumbar axial lig. flavum measure mean	5.85 (5.05-6.32)	6.0 (4.77-6.72)	6.35 (5.37-6.58)	0.656	0.720

Analyzed with the Krukal-Wallis (KW) Test. In the post-hoc Kruskal-Wallis one-way ANOVA test, it was observed that the "Lumbar MRI Axial Spinal Canal AP Measure" measurement of the HY1 group was significantly lower than the HY2 group.

Measurements are given as mm. HY = Hoehn Yahr

positively correlated with the progression of the HY stage. When we looked at the relationship between the HY phase and the canal measurements, it was evident that the Lumbar MRI Axial Spinal Canal Ap measurement was significantly lower in the HY1 group than in the HY2 group ($p = 0.011$).

When looking at the relationship between the group that received and did not receive Parkinson's treatment and the lumbar MRI measurements, no significant difference was found (Table 6).

DISCUSSION

Pain in PD can occur in both treated and untreated PD patients due to the objective pain perception impairment, related to the disease itself, and secondary diseases such as musculoskeletal or visceral pain. The most commonly used clinical classification of pain in PD is the classification proposed by Ford, which divides pain into musculoskeletal, radicular/neuropathic, dystonia-related, akathisic discomfort/pain, and central pain. The prevalence of pain in PD patients ranges from 40-85%. [6, 17-19].

Musculoskeletal problems are the most common cause of physical disability in the general population. Although musculoskeletal problems are common, a few reports describe the prevalence or clinical features of musculoskeletal problems in PD. In a survey on the effect of comorbidities on health-related quality of life (HRQoL) in patients with PD, Andreadou *et al*. reported that arthritis, low back pain, and osteoporosis, musculoskeletal problems (45%) were the most common comorbid disorders in patients with PD [9, 20].

When age increases, degenerative spine problems are also known to increase. The prevalence of disc or posterior facet degeneration increases exponentially after age 50. Bijkerk *et al*. [21] showed that 68.5% of men and 66.2% of women have degenerative disc disease. In addition, Lomber Spinal Stenosis (LSS) is a

Table 6. Measurements in the group that received and did not receive Parkinson's treatment

Parameter	Parkinson's treatment + (n = 15)	Parkinson's treatment – (n = 11)	Z	*p* value
Lumbar MRI sagittal spinal canal measure 1	13.4 (12.2-14.4)	11.6 (9.1-14.35)	0.872	0.392
Lumbar MRI sagittal spinal canal measure 2	12.8 (11.1-14.5)	11.7 (8.4-13.8	0.873	0.392
Lumbar MRI sagittal spinal canal measure 3	12.9 (11.2-13.8)	12.2 (8.57-13.25)	0.743	0.392
Lumbar MRI sagittal spinal canal measure mean	12.96 (12.16-14.83)	11.68 (8.77-11.43)	0.743	0.466
Lumbar MRI axial spinal canal AP measure	11.6 (10.6-15.4)	12.1 (8.55-13.85)	0.775	0.466
Lumbar axial lig. flavum measure 1	6.0 (5.5-6.6)	5.7 (4.82-6.56)	0.775	0.466
Lumbar axial lig. flavum measure 2	6.2 (5.10-5.72)	4.6 (4.02-6.25)	1.774	0.087
Lumbar axial lig. flavum measure mean	6.1 (5.15-6.65)	5.57 (4.75-6.55)	0.840	0.428

Analyzed by Mann-Whitney U test. Measurements are given as mm.

clinical problem that becomes increasingly common as the population ages [4, 21, 22]. The deterioration in the proprioceptive mechanism, which increases with age, causes deterioration in the agonist-antagonist muscles in the joint structure that normally absorb shocks. Moreover, with the concomitant changes in postural control, PD may exacerbate the back problems associated with pre-existing degenerative diseases [4, 23, 24].

In our patients, the most common type of pain was back, hip, and radicular pain. Although 38.5% of patients had lumbar spine surgery, it was remarkable that the most common pain was waist, back, hip, and radicular pain. The most common diagnosis is lumbar radiculopathy with lumbar spinal stenosis, followed by lumbar radiculopathy with failed back surgery. In fact, diagnoses made for pain in the lumbar region have a total share of 57.5% among all diagnoses.

Buhrmann *et al*. [17] stated in a study conducted on PD that 71.4% of patients had back pain, followed by joint pain with 52.4% and that only 15.3% of the pain had a neuropathic character. They showed that pain was independent of the HY stage and that anti-parkinson drugs had a positive effect on their pain in only one-third of patients. Based on this, they stated that it is unlikely that the pain in PD can be solely explained by changes in dopaminergic pathways. Compared to pain frequency, only a quarter of patients were found to be diagnosed for their pain, and pain specialists were involved in only 10.9% of pain treatments, and neurologists - although one of the main treating doctors in PD - were only involved in pain management in 3.3% of cases [17, 25]. This study is similar to our study in that waist and back pain are the most common symptoms. Since our study was retrospective and was performed only on patients who applied to the neurology-pain outpatient clinic, there was no scale given in the follow-up phase regarding the effectiveness of dopaminergic treatment on pain or pain. This is one of the limitations of our study.

In our study, interventional pain therapies were applied to the patients as treatment. These patients were either currently receiving medical therapy or did not benefit from medical therapy. Some patients underwent more than one interventional procedure for pain palliation. In Buhmann *et al*.'s study [17], peripheral nerve blockade (22.6%) was found to be the most common interventional treatment option for pain, followed by epidural injection (8.9%) and infusion (7.3%). They noted that despite the high prevalence of chronic pain, only a quarter of their patients had a formal diagnosis of pain, thus confirming that pain in PD is an undergraded and inadequately treated symptom [17].

If we look at the interventional treatments (Table 3) in our study, epidural injections are the most common 33.2%, followed by facet median bundle branch block and median branch radiofrequency procedures with 23.3%. Vertebroplasty/kyphoplasty was performed on two patients before. In this age group, which also has osteoporosis, we should be careful against pain due to vertebral fracture.

In the geriatric age group with rotoscoliosis, lumbar surgery, posture disorders, it is very difficult to optimally measure the sagittal cross-section from a single level in MRI. For this reason, measurements were made at the lumbar levels most suitable for MRI. This is the reason for the measurements made at different levels in the sagittal section, which is one of the limitations of our study. Foraminal measurements could be more reliable than AP measurement in this patient group, where foraminal stenosis is also common, but MRI sections were not optimal for foraminal measurements. The narrowest level of axial spinal canal measurement was found to be L4-L5.

LSS can be defined both clinically and radiologically. MRI is often used to evaluate the radiological signs of LSS. However, there are no detailed classification criteria for defining LSS using MRI. Indeed, significant variability has been identified in both quantitative, semi-quantitative, and qualitative descriptions. However, as assessed by MRI and clinical symptoms, there appears to be only a weak correlation between spinal morphology. Cautious interpretation of LSS and results has been recommended, as there is considerable variation in defining diagnostic criteria between studies for both clinical symptoms and radiological signs [26-29].

Measurements in our study are shown in Table 4. The differences with the HY stage in Table 5 and the relationship between the groups that received and did not receive Parkinson's treatment are depicted in Table

6. Although our patients comprised both clinically symptomatic and asymptomatic groups with no complaints in the lumbar region, they were predominantly clinically symptomatic. Advanced age, low number of patients, and additional comorbid diseases such as osteoporosis can be considered confounder. Between the HY stage and axial spinal AP measurement, those in the HY1 stage were observed to be significantly lower than those in the HY2 stage. In fact, as the HY stage progresses, the postural disorders are expected to become evident, and axial involvement increases. However, there is a major difference between HY1 and other stages, such as unilateral disease and bilateral disease.

In this case, the question arises whether the mechanical stress increases more in the presence of unilateral disease to ensure stability and the secondary canal diameter is measured smaller with axial measurement. We believe that the staging and measurements of PD patients with low back and leg pain should be investigated in future studies.

There was no significant difference between the groups that received and did not receive PD treatment. Since there is no pain secondary to dystonia, the difference may not be observed. However, the effects of PD treatment, which is also effective on rigidity and axial degeneration, assumes significance. Additionally, back pain is another issue that needs to be investigated in larger numbers. Although studies suggest that LF thickens with age, there are also studies stating that LF thickening is independent of age and gender and that mechanical stress and degeneration are the most important ones [11-13, 30, 31].

It has been stated that LF has different thicknesses at different levels. Kolte *et al*. [11], Altinkaya *et al*. [30], and Abbas *et al*. [31] stated that the thickest level in their study was L4-L5. They demonstrated the increased thickness at the level of L4-L5 instead of L5-S1, the stabilization of the L5-S1 segment with iliolumbar ligaments, and the greater transverse process of the L5 vertebra, in addition to the greater coronal alignment of the S1 facets and the ability to reduce shearing stress. In the study of Kolte *et al*. [11], in the 61-80 age group, right and left LF measurements averaged 4.35 and 4.43 mm, respectively in the thickest L4-L5. In the study of Sakamaki *et al*. [32], the thickest LF in the 60-69 age group was 3.8 mm, and it was 3.9 mm in the 70-79 age group. In the study conducted by Altinkaya *et al*. [30], it was measured as 5.1 mm above the age of 80 and in the thickest segment. In our study, the age group was homogeneous and the mean LF measurement was found to be higher than other studies with 6.05 mm.

Limitations

One of our limitations is ; we could not evaluate the all patients while they are in the ON period. But we enrolled only the chronic pain patients, so ON period can be negligible. Dystonia that painful situation in the ON period were not seen in our patients while examining. Although the absence of a control group in our study is another limitation and also we couldn't get the records of electromyography (EMG), it is noteworthy that the measurements of LF are significantly higher than in other studies. In conclusıon, in our study, LF measurements were found to be thicker in a similar geriatric age group compared to other observed studies. The most common clinical pain syndrome was lumbar stenosis and lumbar radiculopathy. These Parkinson's patients are mostly observed in the geriatric age group. However, are these measurements related to age or axial involvement due to the disease itself? We opine that our study will inspire further studies on this subject. We would also like to draw attention to pain complaints which are non-motor symptoms but are often overlooked.

CONCLUSION

We found that lumbar stenosis and lumbar radiculopathy was the most common clinical pain syndrome in our Parkinson patients. LF measurements in PD were found to be thicker in a similar geriatric age group compared to other observed studies. Pain is an important and often overlooked symptom in PD.

Authors' Contribution

Study Conception: ZTI, FAE; Study Design: ZTI, GGÇ; Supervision: ZTI, SGB; Funding: N/A; Materials: ZTI; Data Collection and/or Processing: ZTI, FAE, GGÇ; Statistical Analysis and/or Data Interpretation: ZTI, SGB; Literature Review: ZTI, FAE; Manuscript Preparation: ZTI, SGB and Critical Review: ZTI, SGB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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