MEDICAL UNIVERSITY OF PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF NEUROLOGY AND NEUROSURGERY

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AGE- AND GENDER-RELATED DIFFERENCES IN NON-MOTOR SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE

Author's abstract to Dissertation

For the award of the degree of Doctor of Education and Science

Supervisor

Assoc. Prof. Dr. Maya Penkova Danovska-Mladenova PhD

Pleven 2024

The dissertation comprises 122 pages and is illustrated with 56 tables and 51 figures.

The bibliography includes 221 literature sources, with 8 in Cyrillic and 213 in Latin script.

The dissertation has been approved and scheduled for defense by an expanded departmental council of the Department of Neurology and Neurosurgery at the Medical University - Pleven. The defense of the dissertation will take place on 04.06.2024 at 12:00 in the "Ambroise Paré" hall at MU - Pleven.

The materials for the defense are available in the Scientific Department and have been published on the website of MU – Pleven – www.mu-pleven.bg.

Brief information about the doctoral student:

Dr. Desislava Marinova graduated in medicine at the Medical University of Pleven in 1992.

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She acquired a specialty in nervous diseases in 1999.

Dr. Desislava Marinova has published three articles related to her dissertation: 1 in JBCR of Medical University- Pleven and 2 in the Journal of Neurology and Psychiatry.

List of abbreviations used:

GID – gastrointestinal disorders

DPD - depression in Parkinson's disease

MD – memory dysfunction

NPS - neuropsychiatric symptoms

NMS - non-motor symptoms

OSA - obstructive sleep apnoea

PD - Parkinson's disease

ICD - impulse control disorder

Sl. D. - sleep disorders

SD - sexual dysfunction

RLS - restless legs syndrome

UD - urinary disorders

RBD – Rapid eye movement sleep behaviour disorder

CVD – cardiovascular disorders

Contents

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease. The disease affects the adult and elderly population. For the last decades, an increase in the mean age of onset worldwide has been noted, i.e., there is an increase in the proportion of the population at risk of developing PD. According to the literature data, the prevalence of PD in the population aged 50 years and over was 4.1-4.6 million in 2005. It is estimated that this number will double to 9.3 million in 2030. In Bulgaria, the estimated number of patients with PD is about 12,000. Clinically, PD manifests with its characteristic motor symptoms: tremors, rigidity, bradykinesia, and postural disturbances. The disease is also characterized by multiple non-motor symptoms (NMS), which play a major role in deteriorating the life quality of PD patients. Unfortunately, NMS are often not actively sought, diagnosed, and adequately treated. Following the extensive study by Chaudhuri K et al. (2006), NMSs have been the subject of well-deserved and intensive study worldwide. Questionnaires for active symptom detection and scales for symptom assessment have been developed in many languages.

In Bulgaria, there is no systematic study of NMS (non-motor symptoms); there is only one study on pain in PD. It has been established that NMS are diverse and numerous. Following an analytical review of data from 221 analytical sources on the issues of non-motor symptoms in Parkinson's disease, including their frequency, gender, and age characteristics, the following aspects of Parkinson's Disease have been discussed:

1. Types of NMS and their clinical characteristics
2. Methods for assessing NMS
3. Frequency of NMS
4. Influence of gender on the frequency of NMS
5. Influence of age on the frequency of NMS
6. Influence of disease stage on the frequency of NMS

Questionnaires for detecting NMS and methods for their assessment have been developed. It is generally agreed that the frequency of NMS is high, around or above 99%. Data on the influence of gender, age, and disease stage on the frequency of NMS are not consistent, both globally and in Bulgaria.

The aim and objectives of the dissertation work were formulated based on the unresolved issues regarding the timely identification, assessment, and therapeutic intervention of NMS in PD.

2. Objective

The present study aimed to investigate the incidence of NMSs and age- and sex-related differences in patients with Parkinson's disease that presented in the specialized PD consulting office at the Clinic of Neurology in Dr. G. Stranski UMHAT – Pleven, affiliated with the Medical University – Pleven, and was carried out at the clinic. The study was carried out in the Neurology Clinic at the same university.

In order to achieve the set goal, the following tasks were defined:

3. Tasks

3.1. To determine the frequency of NMS in patients with PD in the studied group of patients from Bulgaria.

3.2 To determine the mean incidence of each NMS in the PD patients and their frequency according to gender and age.

3.3. To observe the correlation between the frequency of NMS and gender.

3.4. To observe the correlation between the frequency of NMS and the age of patients. 3.5. To observe the correlation between the incidence of NMS and the stage of disease.

4. Material and methods

Clinical material

From a total of 280 patients with PD examined in the Specialized Parkinsonism Clinic between January 2021 and May 2023, 132 patients with NMSD were included in the present study.

The individuals included in the study or their authorized relatives signed an informed consent for participation in the study. The study protocol was approved by the ethics committee at MU-Pleven.

The clinical characteristics of the study patients are presented in Charts 4.1, 4.2, and 4.3

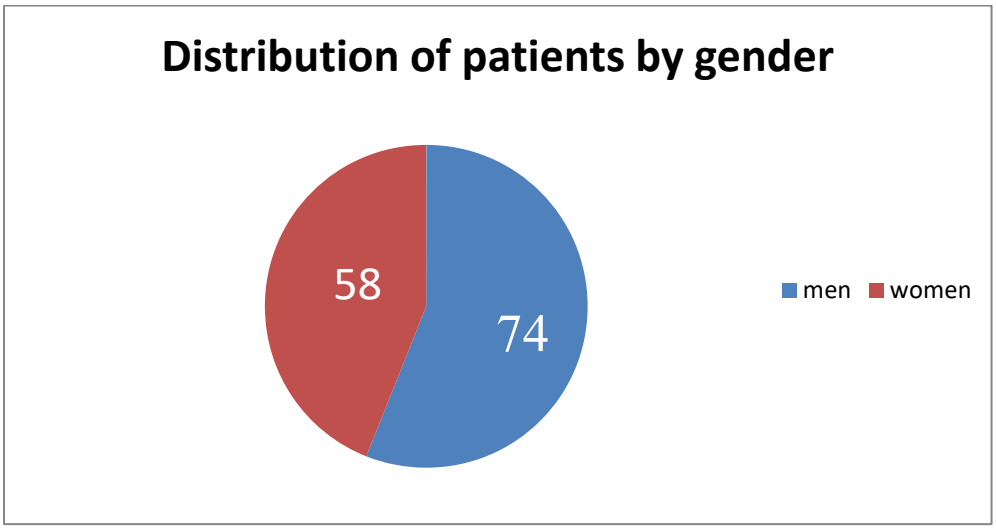

Fig. 4.1. Distribution of patients by gender

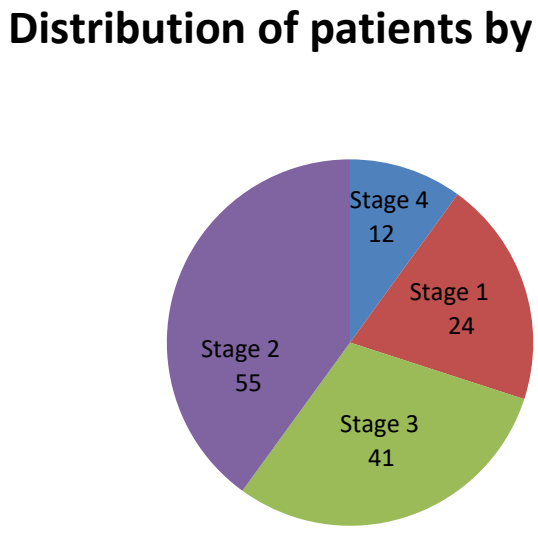

Diagram 4.2. Distribution of patients by stage of disease

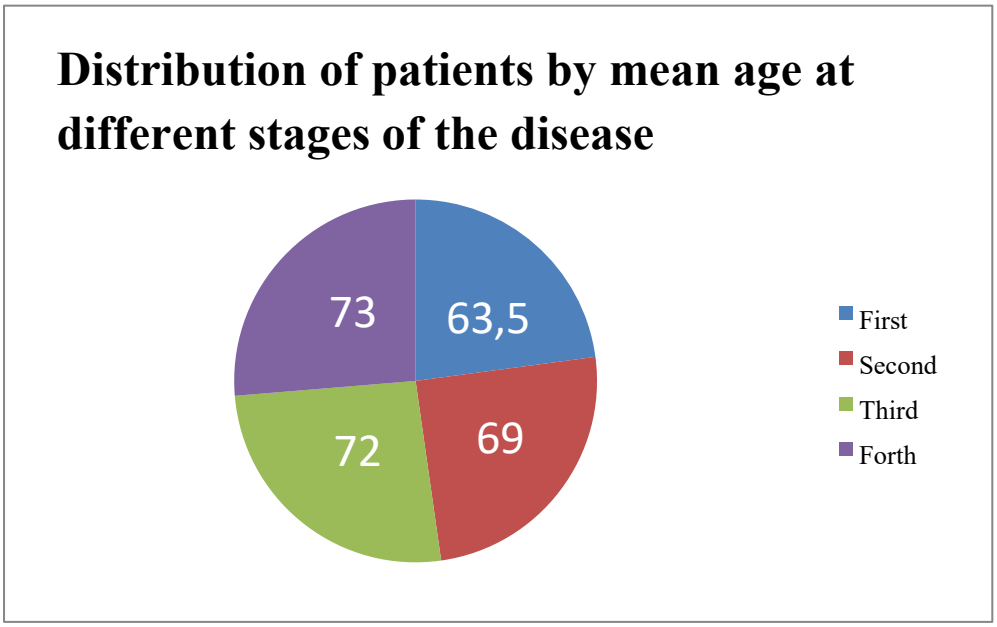

Diagram 4.3. Distribution of patients by age /mean age at different stages of the disease

Regarding mean age, patients in the first and second stages of PD differ by about 6 years, while the mean age for the third and fourth stages is approximately the same.

Inquiry materials

Patient data were entered in forms that reflected the stage of disease according to the Hoehn and Yahr scale (1; 1.5 - 2; 2.5 - 3; 4 - 5).

The diagnosis and stage of PD were determined by two experienced specialists (PhD and MD) using the Unified Parkinson`s Disease Rating Scale part III (UPDRS-III).

A detailed questionnaire to define the stage of the disease and a card including the presence and types of NMSs, the presence and degree of depression, and cognitive impairment. The data were collected after obtaining informed consent from the patients or their relatives.

The questionnaire and scales used for the study are included in the appendices.

In the questionnaire, the available NMSs of PD were grouped into the following 15 sections: gastrointestinal disturbance; pain; cardio-vascular symptoms; sleep dysfunction; apathy; fatigue; urogenital disorders; skin symptoms; neuropsychiatric symptoms; respiratory dysfunction; sensory dysfunction; sexual dysfunction; weight change; depression; cognitive decline.

The degree of memory dysfunction - cognitive decline was determined with the Mini-Mental State Examination (MMSE) and the Isaac`s Set Test of Verbal Fluency (IST). The Hamilton Depression Scale (HAM-D) was used to identify depression.

A detailed questionnaire was designed to define the stage of the illness, and a card including the presence and types of NMS; presence and degree of depression, and cognitive impairment.

Statistical methods

The obtained results were processed statistically using Statgraphics Plus. Parametric data showed a normal distribution and an F-test was used to assess the presence of statistically significant differences between the mean values of the parameters studied. Values of $p<0.05$ were considered statistically significant. The presence of a statistically significant correlation between categorical data was performed using an X-squared test; $p<0.05$ was considered statistically significant.

5. Results

We investigated 132 cases:74 males and 58 females. The median age of the two groups differed significantly (K-W = 8.3285, p=0.0039), with a median of 67 years (range 49 to 84) for males and 72 years (range 48 to 86) for females.

5.1. Distribution of patients by sex, age, and stage of disease

For brevity and clarity in the figures, stages are denoted as first (1), second (1.5-2), third (2.5-3), and fourth (4-5). We found no statistically significant association between gender and disease stage chi-square=0.23; Df=3; p=0.9724.

Stage	Men	Women
1	14 (10.61%)	10 (7.58%)
1.5 - 2	31 (23.48%)	24 (18.18%)
2.5 - 3	23 (17.42%)	18 (13.64%)
4 - 5	6 (4.55%)	6 (4.55%)

Tabl. 5.1. Distribution of patients by sex and stage of disease

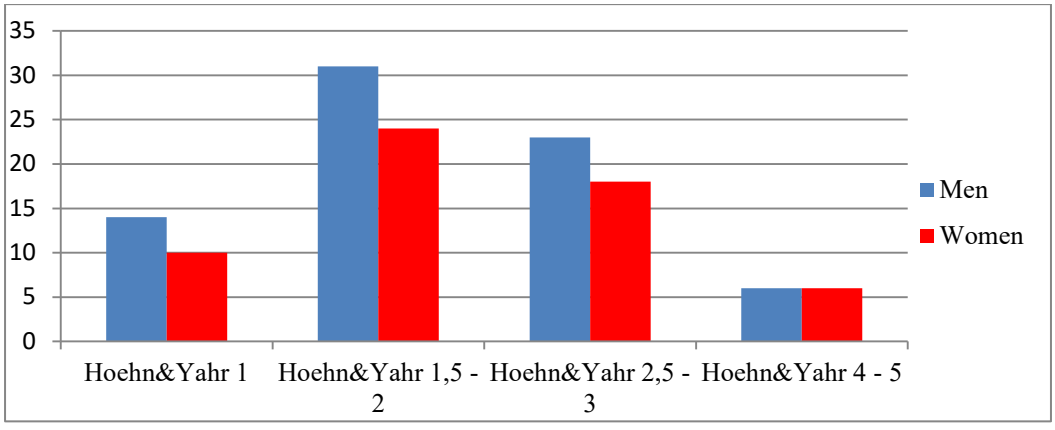

Fig.5.1.1. Distribution of patients by sex and stage

There were 24 patients (18.18%) in stage 1, 55 (41.67%) in stage 2, 41 (31.06%) in stage 3, and 12 (9.09%) in stage 4. The distribution of age and stage of the disease showed statistically significant differences (K-W= 24.0971, p<0.0001).

Stage	Number	Median age	Age range
First	24	63.5	52 - 73
Second	55	69	48 - 80
Third	41	72	57 - 86
Fourth	12	73	59- 79

Tabl. 5.1.2. Distribution of patients by age and stage

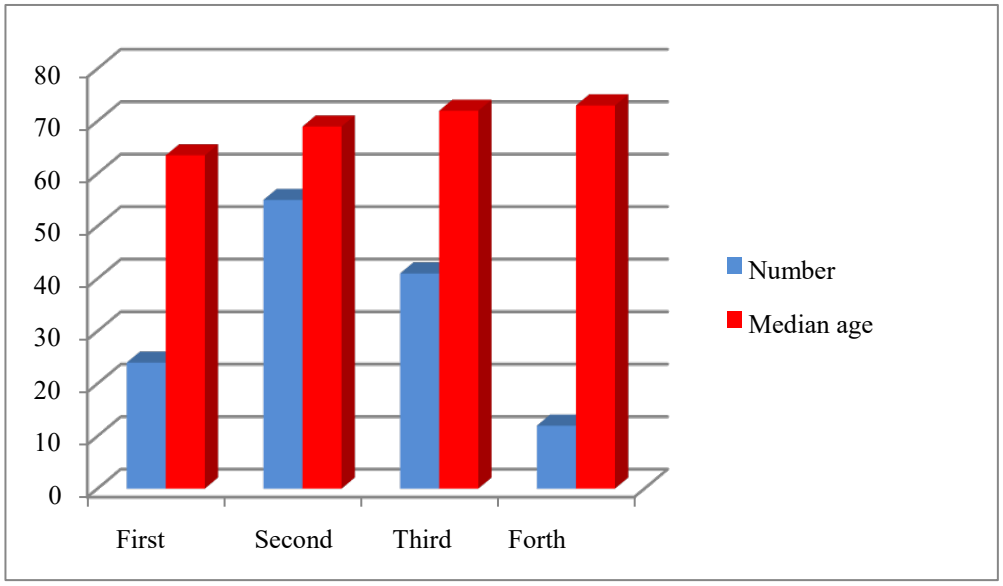

Fig.5.1.2. Distribution of patients by age and stage

Patients in stage one were significantly younger (63.5 years) compared to patients in stage two (69 years), stage three (72 years) and stage four (73 years).

5.2. Incidence of NMS in patients with PD

All of the examined patients exhibit non-motor symptoms, most commonly as a combination of several symptoms. Only one patient has a single non-motor symptom.

The distribution of non-motor symptoms in the studied patients (up to 3; between 4 and 9 and 10 or more symptoms) showed that the males had more NMS on average.

There was no statistically significant association in the gender distribution of cases by number of non-motor symptoms present (up to 3; between 4 and 9 and 10 or more symptoms) chi-square= 0.18; Df=2; p=0.9157.

Non-motor symptoms	Men	Women
up to 3	5 (3.79%)	5 (3.79%)
between 4 and 9	24 (18.18%)	19 (14.39%)
10 and more	45 (34.09%)	34 (25.76%)

Tabl. 5.2. Distribution by mean number of NMSs and gender

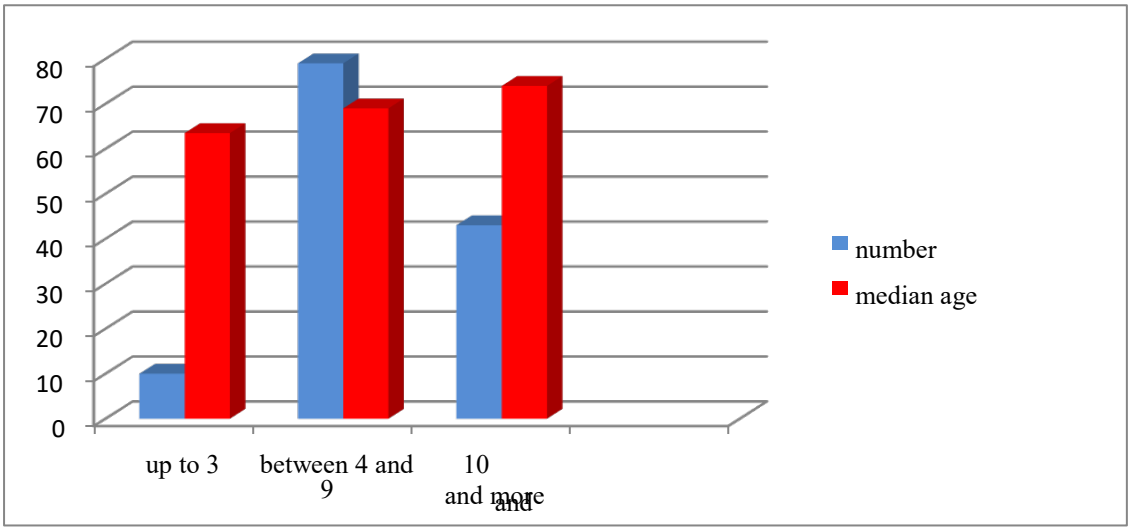

Fig.5.2 Distribution by mean number of NMSs and age

Discussion: Non-motor symptoms are common but, in many cases, undiagnosed and untreated for various reasons - unreported by patients and/or unattended by treating physicians. More than 200 years had to pass before non-motor symptoms received their deserved attention. It is important to note the contribution of Chaudhuri K et al. (2006) to the description and the study system of NMSs. Currently, numerous studies are aimed at both the incidence of NMS and the refinement of methods to study them. There is no comprehensive study of NMSs in Bulgaria; only one detailed study on pain in PD has been published [211].

5.3. Incidence of individual NMSs

Our results showed that all PD patients (100%) had one or more NMSs. Fernandes et al. (2021) also found a high frequency(88.5% of patients with at least one NMS). There are other reports on the 100% frequency of NMSs.

According to the literature, the incidence of NMSs is high and ranges around and above 90%. When we followed the number of NMSs in individual patients, we found that more than half of them - 79 (56.06%), had 10 or more symptoms.

Regarding the frequency of individual NMSs, there was a wide variability.

The most frequent NMSs in our patients were pain, cognitive disorders, symptoms from urogenital and gastrointestinal systems, and sleep disorders, ranging from **65.90% to 82.57%.**

5.3.1. Pain

The pathogenesis of pain in PD is not fully understood. In most cases, it is associated with motor symptoms. However, there are observations that it may be present in the disease's earliest and/or prodromal phases and may precede motor symptoms over the years. Pain in PD has recently been the subject of intense research, including developing the Pain Scale.

The highest prevalence of pain was found in 109 patients (82.57%). Shoulder pain predominated, alone or combined with other symptoms, in 59 patients (44.69%). Stoyanova-Pirot et al. (2021) found that 79.6% of pain, particularly musculoskeletal pain, was predominant in a study of this symptom in PD patients in Bulgaria. The incidence of pain varies over a wide range according to literature data - 40.0% - 95.0% . The data reported by Silverdale M et al. (2018) are the closest to ours, i.e., 85.0% in a study of 1957 PD patients.

5.3.2. Cognitive impairment

The morphological substrate and pathogenesis of cognitive impairment are related to the etiopathogenesis of PD - loss of dopaminergic neurons in the substantia nigra and deposition of α-synuclein and "Lewy bodies." The loss of dopaminergic neurons in parietal, frontal, and temporal cortical areas is associated with cognitive impairment.

Memory impairment was the second most common disorder, with 97 cases (73.49%). The reported incidence of memory disturbances varies across reports due to the use of different methods and according to the stage of the disease. The usual incidence ranges between 30% and 40%. Pedersen K et al. (2017) found 28.9%, and Baiano C et al. (2020) - 31%. Hely M A et al. (2008) found a high incidence of dementia (83.0%) but after a 20-year disease duration. It should be noted that despite the large number of patients with memory disorders in our material, mild forms were recognized in all cases.

5.3.3. Urogenital symptoms

Symptoms of lower urinary tract problems are also associated with morphological changes in the central and autonomic nervous systems in PD. As is well known, bladder function is associated with complex neuro-regulatory mechanisms whose centers are affected by α-synuclein deposition and "Lewy bodies". Furthermore, urinary disturbances may be related to the disease or result from antiparkinsonian treatment. Depending on the level of involvement in the different levels of neural regulatory centers, micturition disorders present with two main symptoms: obstructive and irritative. According to the literature, the incidence of this NMS varies but is relatively high. Valentino F. et al. (2018) found an incidence of 93.8%. Similar results were reported by Martinez-Ramirez D. (2020) - 94.7% in a group of 447 PD patients, and by Xu D et al. (2019) - 89%. Based on literature data and meta-analyses involving 14,937 PD patients, Li F-F. et al. (2022) found a mean incidence of urinary tract disturbances of 61%. The incidence of micturition disorders in our patients was 68.93%. Irritative symptoms, represented by nocturnal urination, predominated - 60.60%.

5.3.4 Gastrointestinal disorders (GID)

Gastrointestinal disorders in PD are among the most common NMSs, and they significantly contribute to the impairment of life quality. Some GIDs, such as dysphagia, can be life-threatening conditions as a prerequisite for aspiration pneumonia and death. J.Parkinson also mentioned dysphagia as a sign of the disease he described. Because of their high frequency and contribution to patient discomfort, they have been studied extensively and documented in numerous publications. A specific scale for the assessment of GID has also been established. Morphological changes in the enteric nervous system are discussed for the pathogenesis of GID. According to the hypothesis of Braak et al., an unknown pathogen enters through the digestive tract and gives rise to the so-called Lewy pathology.

Data on the prevalence of GI in PD indicate a higher prevalence than those unaffected by PD, reaching up to 80%. Lubomski M. et al. (2020), in a study of 103 PD patients, found a threefold higher prevalence of constipation compared to 81 controls (78.6% vs. 28.4%), as well as more frequent and pronounced symptoms of nausea, vomiting, etc. The prevalence of GI D was lower in our patients (66.66%). The prevalence of constipation was 53.27%.

5.3.5 Sleep disorders

The pathogenesis of sleep disorders is complex and complicated. Apart from the pathogenesis of the underlying disease, especially with motor and NMSs (e.g., nycturia), some other factors have an impact, such as circadian rhythm disturbance, therapy administered, etc. In most cases, a combined effect is involved. Sleep disorders are diverse and include symptoms such as daytime sleepiness, insomnia, psychotic symptoms during sleep, etc. Sleep disturbances in our study were found in 65.90% of patients. Insomnia was the most frequent - 46.96%.

The data on the frequency of insomnia and its individual manifestations in the literature are variable and range from 37.0% to 80.0%.

5.3.6 NMSs with a prevalence greater than 50%

Other NMSs with an incidence above 50.0% are fatigue, neuropsychiatric symptoms, cardiovascular symptoms, and depression.

5.3.6.1 Fatigue

The prevalence of fatigue in our study contingent was 59.09%. Fatigue is a subjective sign and can be defined as an overwhelming feeling of tiredness, lassitude, lack of energy, and exhaustion (subjective fatigue). Objective fatigue is defined as a mixture of expended effort or a reduced ability or lack of ability to perform or sustain any volitional activity . Most patients do not report fatigue or it is not detected even by profiled specialists.

Its prevalence in the study contingent was 59.09%. Data on the prevalence of fatigue in PD vary due to the lack of uniform criteria for the symptom and the lack of sufficiently specific assessment scales (28%-58%). Based on data from a systematic review of the literature and meta-analyses (2459 titles), Siciliano M et al. (2018) found a mean prevalence of fatigue in PD patients of 50%.

5.3.6.2 Neuropsychiatric symptoms

Psychotic symptoms are common in PD patients and range up to 40% depending on the methods and criteria used, as well as the stage of the disease. These manifestations are assumed to be treatment-related, but there have been observations of early preclinical psychotic manifestations, suggesting a pathogenetic link to the underlying disease. The mean incidence of neuropsychiatric symptoms in our study patients was 58.33%. No hallucinations were found in any case. Depression and sadness were the most frequent symptoms. Depression will be discussed further.

5.3.6.3 Cardiovascular symptoms

Cardiovascular (CV) symptoms in PD are not very common, but important because they are relevant not only to quality of life but also to morbidity and mortality in PD patients. The mean incidence of CV symptoms in our patients was 57.58%; the predominant sign was orthostatic hypotension. No serious life-threatening symptoms were found.

5.3.6.4 Depression

The objectification of depression in PD is a diagnostic challenge. Clinically, depression is characterized by feelings of guilt, worthlessness, sadness and dissatisfaction, and lack of self-esteem. Some somatic signs, such as a mask-like face, motor retardation, loss of appetite, and weight loss may also be present. These symptoms may also be present in patients without depression, overlapping with other NMSs

and making the diagnosis of depression difficult, leading to a hypo- or hyperdiagnosis. In our study, we used the Hamilton depression scale for diagnosing depression. Literature data on the prevalence of depression range from 27% to 90%. In a more recent, extensive literature review that included 129 publications from 28 countries with 38 304 PD patients, Cong S et al. (2022) found that the mean prevalence of depression in PD was 38%. The mean prevalence of depression in the patients studied was 53.03%. This incidence is slightly higher than reported in the literature, but it is noteworthy that mild degrees predominate, 41.66%.

5.4 Incidence of individual NMS according to gender

Most frequent NMS, on average and according to gender

According to the data obtained, the average frequency of individual NMS is as follows.

Overall, for both male and female groups, the most frequent NMSs are:

1.	Pain	109 cases	82,57 %
2.	Cognitive disorders	97 cases	73,49 %
3.	Urogenital symptoms	91 cases	68,93 %
4.	Gastrointestinal symptoms	88 cases	66,66 %
5.	Sleep disturbances	87 cases	65,91 %

For men, the most common NMS were:

1.	Pain	60 cases	81,08 %
2.	Urogenital symptoms	55 cases	74,32 %
3.	Gastrointestinal symptoms	54 cases	72,97 %
4.	Cognitive disorders	53 cases	71,62 %
5.	Sleep disturbances	51 cases	68,91 %

In women, the most common NMS were:

1.	Pain	51 cases	84,48 %
2.	Gastrointestinal symptoms	46 cases	79,00 %
3.	Cognitive impairment	44 cases	75,86 %
4.	Cardiovascular disorders	43 cases	74,13 %
5.	Urogenital symptoms and sleep disorders	36 cases	62,06 %

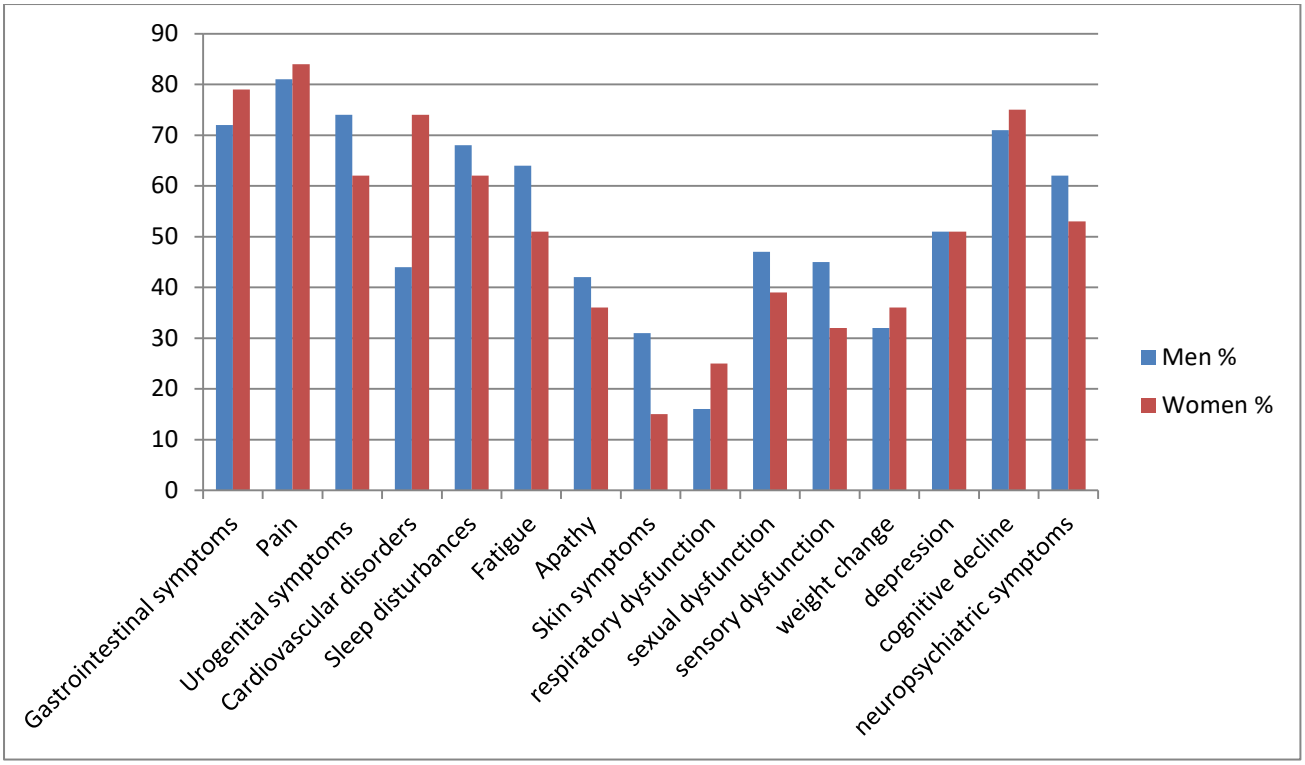

Fig. 5.4.1. Incidence of NMS by sex

By gender, there is some variation in the prevalence of NMS, but for both genders, pain is the leading cause.

5.4.1 Gastrointestinal (GI) symptoms

Patients were analysed in three groups: with no symptoms, one leading symptom, and two or more leading symptoms. There was no significant difference between gender and GIT symptom scores. chi-square=2.93. Df=2, p= 0.2311

Gender	Without symptoms	With one leading symptom	With two or more leading symptoms
Men	20 (15.15%)	16 (12,12%)	38 (28,79%)
Women	22 (16.67%)	7 (5,30%)	29 (21,97%

Tabl. 5.4.1. Prevalence of GIS according to gender and number of symptoms

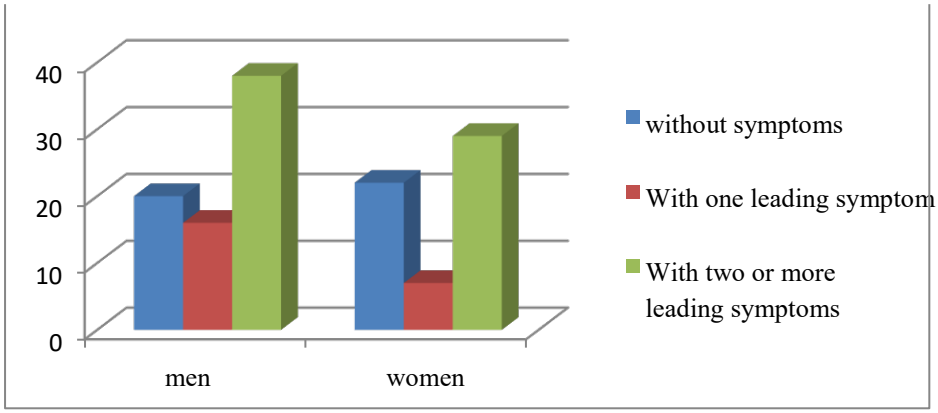

Fig. 5.4.1. Prevalence of GIS according to gender and number of symptoms

There were 42 (31.82%) patients without symptoms, 23 patients (17.42%) had one leading symptom, and 67 patients (50.76%) had two or more leading symptoms. The most common symptom was constipation, alone or in combination with other symptoms (in 59 cases).

6.4.2 Pain

The presence of pain symptomatology showed no statistically significant association between the categories studied: chi-square=0.08, Df=1, p=0.7793.

Gender	Without pain	With pain
Men	14 (10.61%)	60 (45,45%)
Women	9 (6.82%)	49 (37,12%)

Tabl. 5.4.2. Frequency of pain symptoms by gender

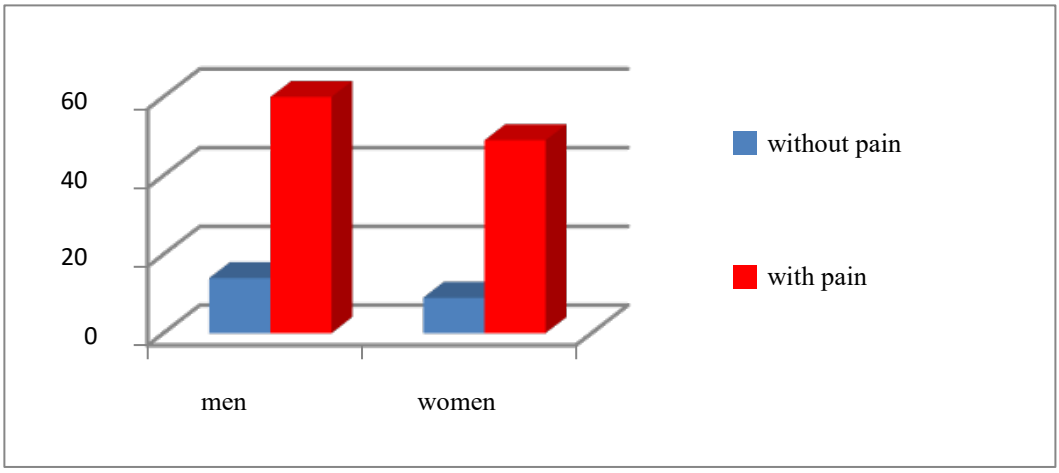

Fig. 5.4.2. Frequency of pain symptoms by gender

Pain was present in 109 (82.58%) of the cases. Shoulder pain, alone or combined with other symptoms, predominated (in 59 patients).

5.4.3. Urogenital symptoms

There was no association between the gender distribution of cases and the presence of urinary symptoms: chi-square=1.74, Df=1, p=0.1866.

Gender	Without urinary tract disorders	With urinary tract disorders
Men	19 (14,39%)	55 (41,67%)
Women	22 (16.67%)	36 (27,27%)

Tabl. 5.4.3. Incidence of urinary symptoms by gender

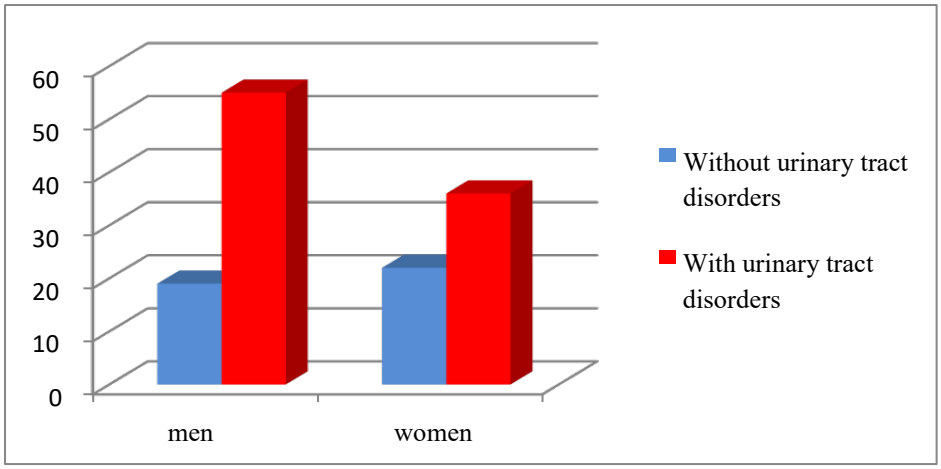

Fig. 5.4.3. Incidence of urinary symptoms by gender

In 91 (68.94%) cases, urinary tract disorders were present. The most common symptom was frequent nocturnal urination, alone or in combination with other symptoms (in 80 of the cases).

5.4.4. Cardiovascular disorders (CVD)

There was a significant association between sex distribution and cardiovascular symptoms: chi-square=10.44, Df=1; p=0.0012. CVDs were more frequent in women.

Gender	Without CVD symptoms	With CVD symptoms
Men	41 (31,06%)	33 (25,00%)
Women	15 (11,36%)	43 (32,58%)

Tabl.5.4.4. Incidence of CVD according to gender

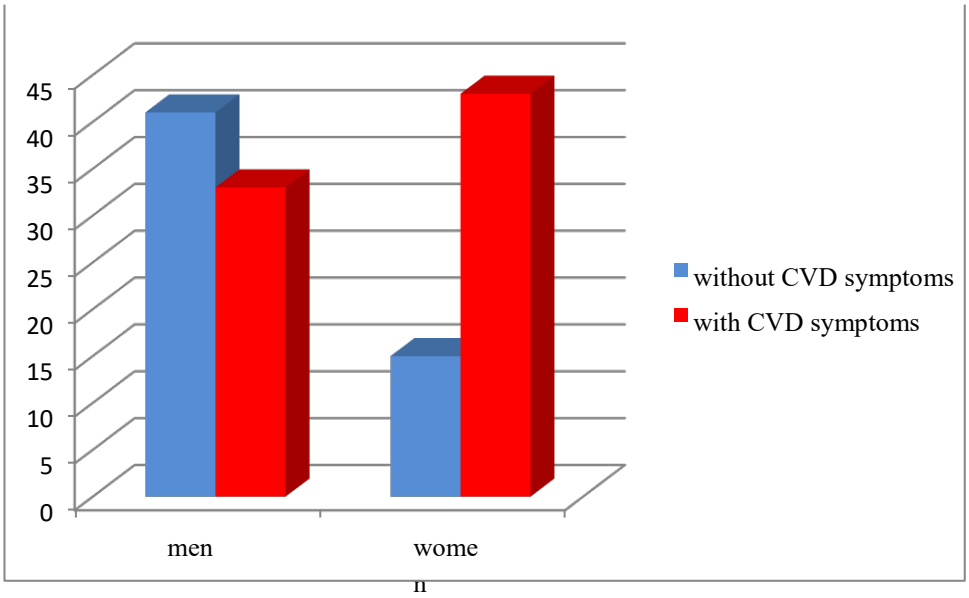

Fig.5.4.4. Incidence of CVD according to gender

Cardiovascular diseases were present in 76 (57.58%) cases. The most common symptom was dizziness on standing, observed alone or in combination with other symptoms (64 cases).

5.4.5 Sleep disturbance

There was no correlation between gender and sleep disturbances in the studied patients: chi-square=0.41, Df=1, p=0.5228.

Gender	Without sleep disturbance	With sleep disturbance
Мъже	23 (17.42%)	51 (38.64%)
Жени	22 (16,67%)	36(27,27%)

Tabl. 5.4.5 Frequency of sleep disturbances according to gender

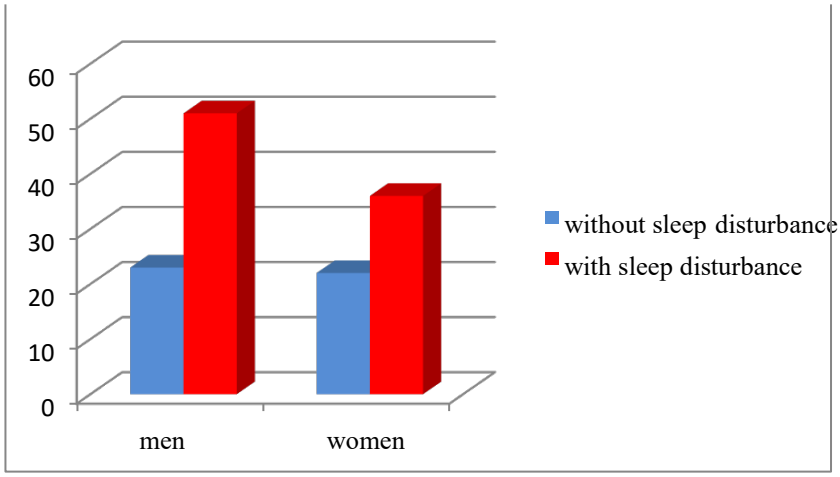

Fig. 5.4.5 Frequency of sleep disturbances according to gender

Sleep disturbances were present in 87 (65.91%) of the cases. The most common symptom was insomnia (in 62 cases) as a stand-alone symptom and in combination with other symptoms.

5.4.6. Fatigue

Although fatigue was more frequent in males, there was no statistically significant correlation between gender and the presence of fatigue in the studied patients: chi-square=1.81, Df=1, p=0.1784.

Gender	**Without manifestations of fatigue**	**With manifestations of fatigue**
Men	26 (19.70%)	48 (36,36%)
Women	28 (21.21%)	30 (22,73%)

Tabl. 5.4.6. Frequency of fatigue symptom according to gender

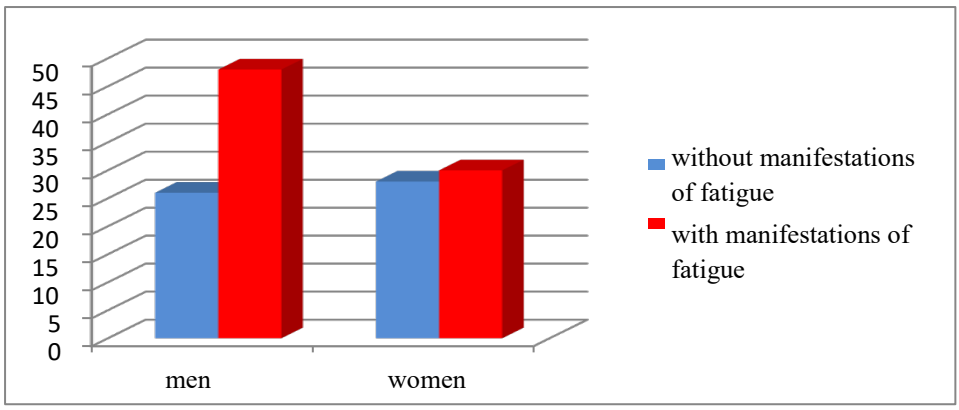

Fig. 5.4.6. Frequency of fatigue symptom according to gender

Fatigue was present in 78 (59.09%) of the cases.

5.4.7. Apathy

The symptom was more frequent in males, but there was no statistically significant correlation between gender and the presence of symptoms of apathy in the studied patients: chi-square=0.41, Df=1, p=0.5224.

Gender	without manifestations of apathy	with manifestations of apathy
Men	42 (31.82%)	32 (24,24%)
Women	37 (28.03%)	21 (15,91%)

Tabl. 5.4.7. Manifestation of apathy by gender

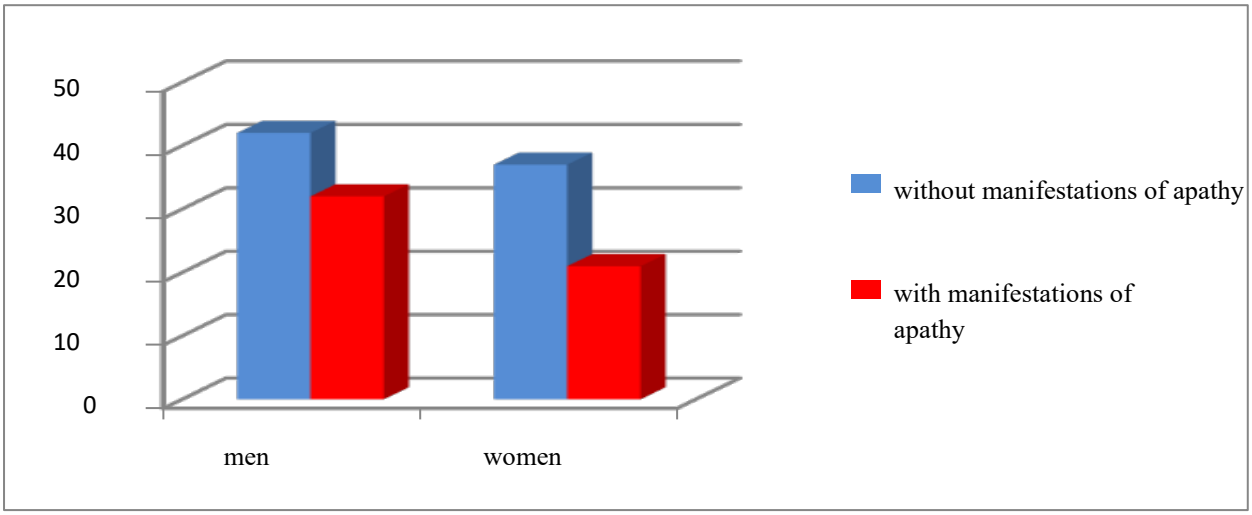

Fig. 5.4.7. Manifestation of apathy by gender

Apathy was present in 53 (40.15%) of the cases. The most common symptom was loss of interest in daily thoughts and activities, observed alone or in combination with other symptoms (in 45 cases).

5.4.8. Skin symptoms

There was a correlation between gender and the presence of seborrhoea and/or hyperhidrosis in the patients studied. Skin symptoms were more frequent in males (21.97% versus 6.82%): chi-square=7.77, Df=1, p=0.0053.

Gender	**Without seborrhea and hyperhidrosis**	**With seborrhea and/or hyperhidrosis**
Men	45 (34.09%)	29 (21,97%)
Women	49 (37.12%)	9 (6, 82%)

Tabl. 5.4.8. Distribution of skin symptoms according to gender

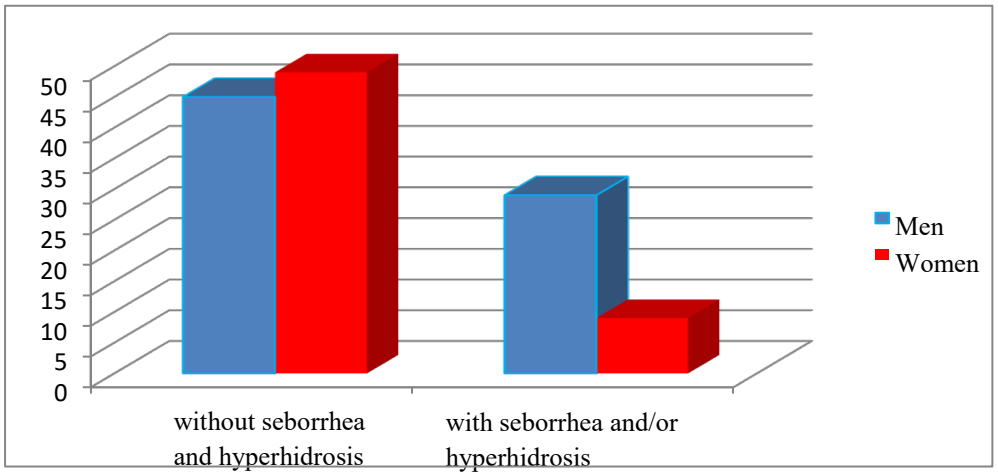

Fig. 5.4.8. Distribution of skin symptoms according to gender

Skin symptoms were present in 38 (28.79%) of the cases. The most common symptoms were seborrhoea and hyperhidrosis (in 25 cases each), alone or in combination.

5.4.9. Neuropsychiatric symptoms

No significant association was observed between sex distribution and the presence of psychiatric symptoms: chi-square=0.69; Df=1; p=0.4065

Gender	**Without psychiatric symptoms**	**With psychiatric symptoms**
Men	28 (21,21%)	46 (34,85%)
Women	27 (20.45%)	31(23,48%)

Tabl. 6.4.9. Distribution of neuropsychiatric symptoms by sex

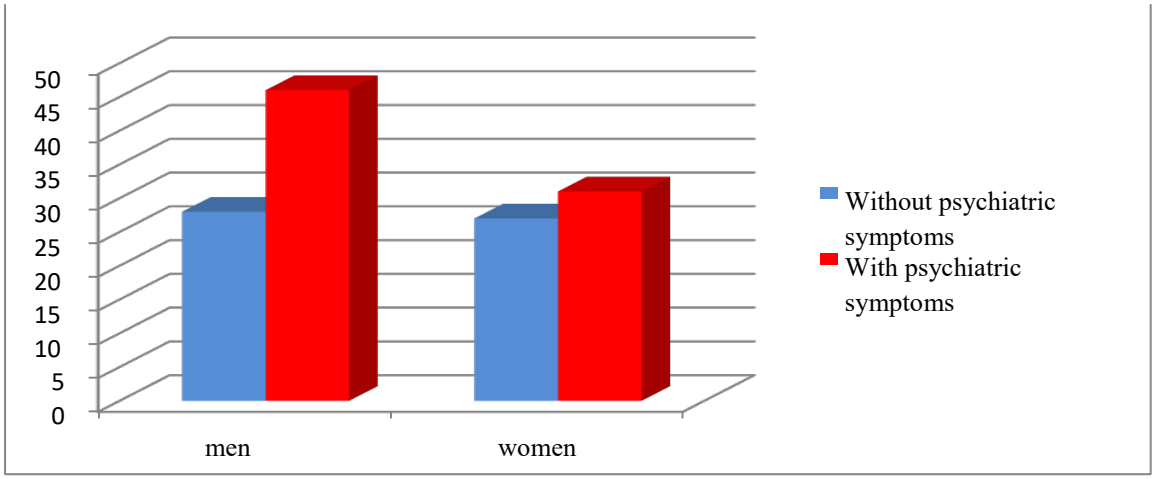

Fig.5.4.9. Distribution of neuropsychiatric symptoms by sex

Psychiatric manifestations were present in 77 (58.33%) of the cases. Sadness and depression were the most common symptoms (in 42 cases), mostly in combination with several other symptoms.

6.4.10. Respiratory symptoms

There was no significant association between sex distribution and the presence of respiratory symptoms: chi-square=1.31; Df=1; p=0.2517.

Gender	No respiratory symptoms	With respiratory symptoms
Men	62 (46,97%)	12 (9,09%)
Women	43 (32,58%)	15 (11,36%)

Tabl. 5.4.10. Frequency of respiratory symptoms according to gender

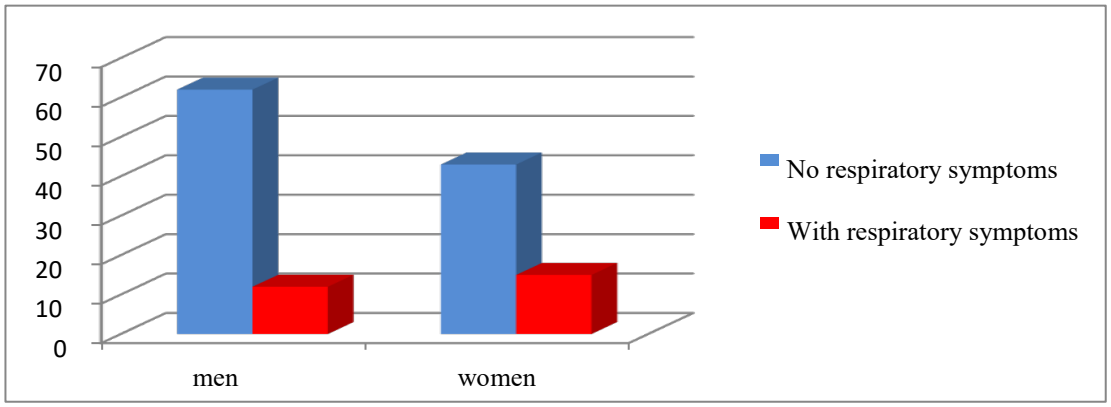

Fig.5.4.10. Frequency of respiratory symptoms according to gender

Respiratory problems were present in 27 (20.45%) of the cases. The most common symptom was cough (in 17 cases), often in combination with other symptoms.

5.4.11. Sexual disorders

There was no statistically significant difference in the distribution of sexual disorders by sex: chi-square=1.35, Df=1, p=0.2453.

Sexual disorders	Men	Women
No sexual disorders	36 (27,27%)	38 (28,79%)
With sexual disorders	35 (26,52%)	23 (17,42%)

Tabl. 5.4.11. Incidence of sexual disorders by gender

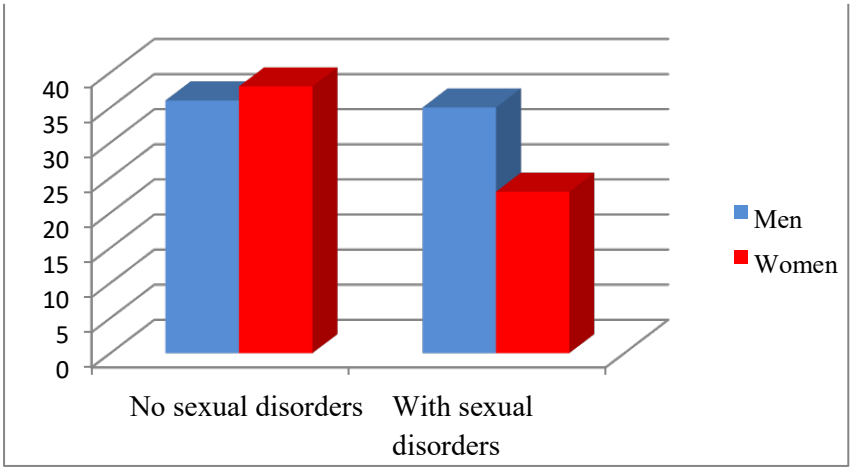

Fig. 5.4.11. Incidence of sexual disorders by gender

Sexual dysfunction was present in 58 (43.94%) of the cases.

6.4.12. Sensory disorders

No significant relationship was observed between gender distribution and the presence of sensory disorders: chi-square=1.84; Df=1; p=0.1754

Gender	Without sensory impairment	With sensory impairment
Men	40 (30,30%)	34 (25,76%)
Women	39 (29.55%)	19 (14,39%)

Tabl. 5.4.12. Prevalence of sensory impairment by gender

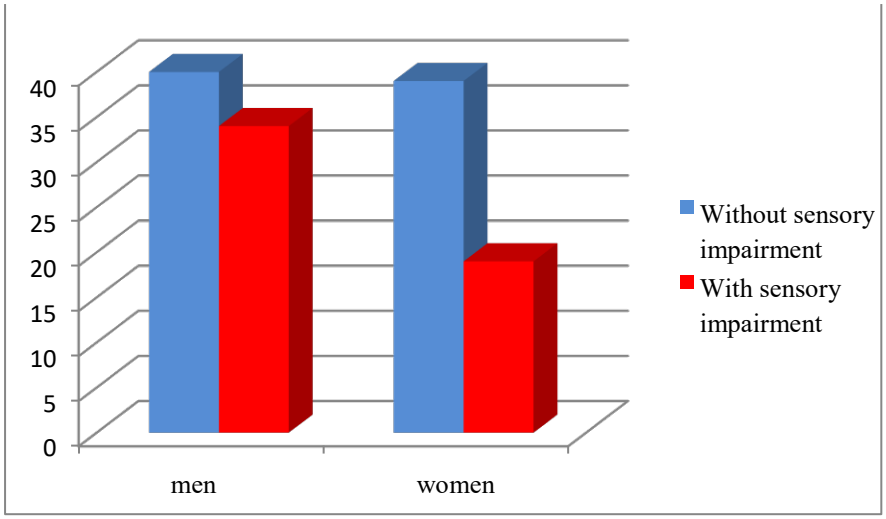

Fig.5.4.12. Prevalence of sensory impairment by gender

Sensory impairment was present in 53 (40.15%) of the cases. The most common symptom was hyposmia (in 45 cases, most often as a stand-alone symptom in 23 cases) or in combination with dysgeusia (in 22 of the cases).

5.4.13. Change in weight

No significant association was observed between sex distribution and the presence of weight change: chi-square=0.07; Df=1; p=0.7879

Gender	No weight change	With weight change
Men	50 (37,88%)	24 (18,18%)
Women	37 (28.03%)	21(15,91%)

Tabl. 5.4.13. Frequency of weight change by gender

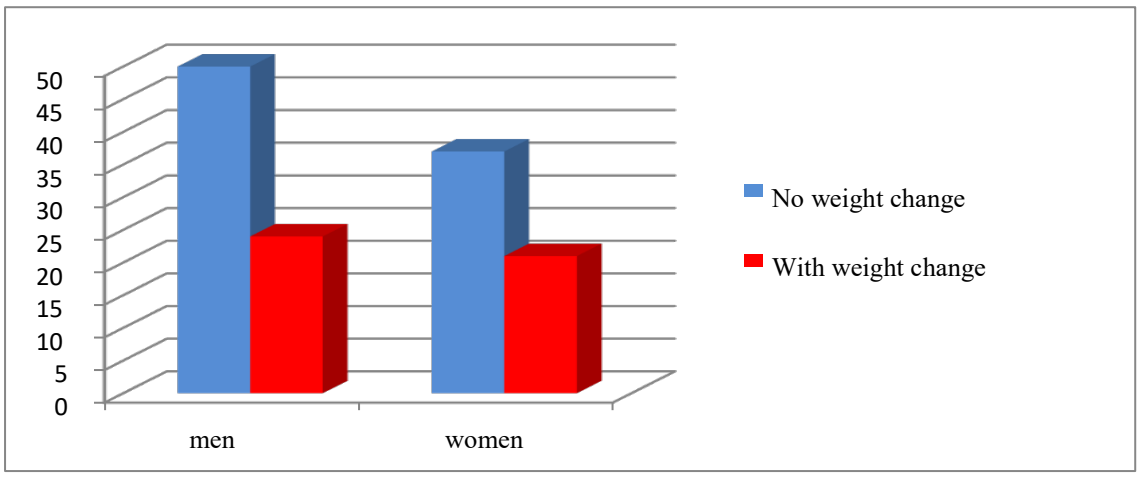

Fig. 5.4.13. Frequency of weight change by gender

In 45 (34.09%) cases, weight change was present with a tendency towards slight reduction.

5.4.14. Depression

There was no statistically significant association between gender and the presence and severity of depressive changes: chi-square=3.14; Df=3; p=0.3709.

Depressive disorders	Men	Women
Missing	36 (27.27%)	26(19.70%)
Mild	27(20.45)	28 (21.21%)
Moderate	7 (5.30%)	3 (2.27%)
Severe	4 (3,03%)	1 (0.76%)

Tabl. 5.4.14. Distribution of degrees of depression according to gender

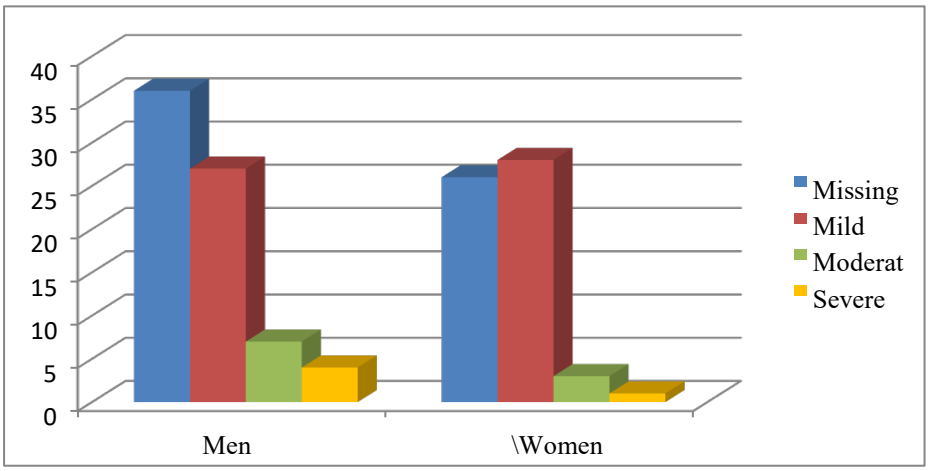

Fig. 5.4.14. Distribution of degrees of depression according to gender

5.4.15. Cognitive impairment

Cognitive impairment was present in 97 (73.49%) cases in varying degrees of severity.

There was no statistically significant relationship between the presence and severity of cognitive impairment in either sex: chi-square=0.69; Df=3; p=0.8760 .

Cognitive disorders	Men	Women
Absent	21 (15.91%)	14(10.61%)
Mild	48 (36,36%)	41(31.06%)
Moderate	4 (3.03%)	2 (1.52%)
Severe	1(0,76%)	1 (0.76%)

Tabl. 5.4.15. Distribution of cognitive impairment by severity and gender

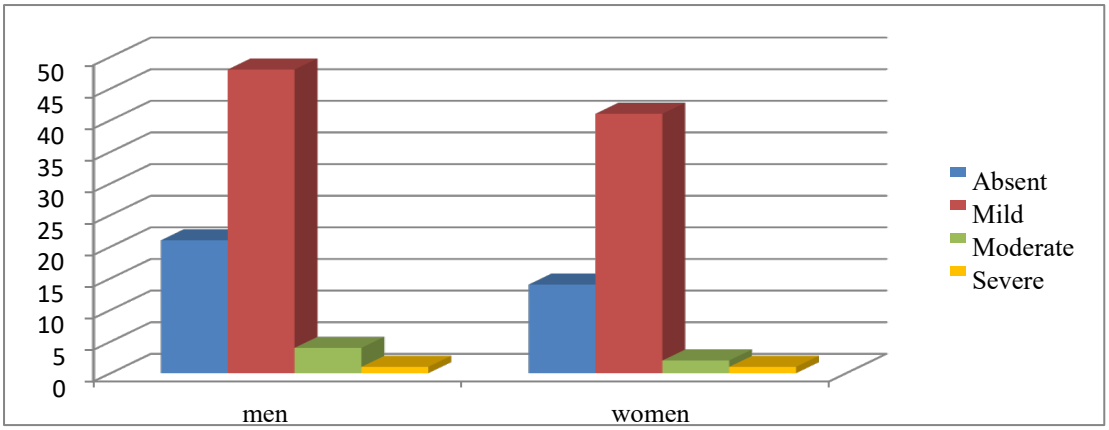

Fig.5.4.15. Distribution of cognitive impairment by severity and gender

5.4.16. Discussion

The influence of gender on motor symptoms of Parkinson's disease (PD) is relatively well-known and is reflected in a number of studies. Information regarding the influence of gender on non-motor symptoms of Parkinson's disease (NMS-PD) is more scarce and contradictory. Some studies show significant differences in the frequency of NMS associated with gender, while others do not. There are also differences in the predominance of certain NMS.

Men are affected by PD two to three times more often than women, but women show faster progression and higher mortality rates. For men, gastrointestinal disorders, daytime sleepiness, and sexual disorders are predominant. Nicoletti A et al. (2017) found a significant difference associated with gender. Women have a higher frequency of depression and urinary disorders, while men more often suffer from sleep disturbances, hallucinations, and cognitive disorders. According to an extensive study by Martinez-Martin et al., which included 951 PD patients, women have a higher frequency of fatigue, depression, constipation, pain, sensory disturbances, and excessive sweating. Decreased olfactory function and increased daytime sleepiness are more common NMS in men, while pain is more frequent in wome. Study data show more frequent disruption of sexual and cognitive functions in men and a higher frequency of depression in women. There are fewer observations of no gender differences. For example, in studies by Abraham et al. (2019), no difference in the frequency of NMS by gender was found, even with disease progressio.

In the current study, differences in the predominance of specific NMS were found according to gender.

For men, the most common NMS are: pain - 81.08%; urogenital symptoms - 74.32%; gastrointestinal symptoms - 72.97%; cognitive disorders - 71.62%; and sleep disturbances - 68.91%.

For women, pain is also the most common - 84.48%, followed by gastrointestinal symptoms - 79.00%; cognitive disorders - 75.86%; cardiovascular symptoms - 74.13%; and sleep disturbances and urogenital symptoms - both 62.06%.

However, these differences are not statistically significant. Significant gender difference was found only for some symptoms:

Cardiovascular symptoms predominate in women. There is a significant relationship between gender distribution and the presence of cardiovascular symptoms: chi-square=10.44, Df=1; p=0.0012.

In 76 (57.58%) of cases, cardiovascular diseases are present. The most common symptom is dizziness upon standing, observed either alone or in combination with other symptoms (in 64 cases).

Skin symptoms. Seborrhea and hyperhidrosis predominate in men. There is a correlation between gender and the presence of seborrhea and/or hyperhidrosis in the studied patients: chi-square=7.77, Df=1, p=0.0053. In 38 (28.79%) of cases, skin symptoms are present. The most common symptoms are seborrhea and hyperhidrosis (in 25 cases each), either alone or in combination.

5.5. Age distribution of individual NMS

		Age									
	Symptom	40-49	%	50-59	%	60-69	%	70-79	%	80-89	%
1	Gastrointestinal symptoms	1	0.76%	13	9.85%	26	19.70%	47	35.61%	3	2.27%
2	Pain	3	2.27%	16	12.12%	32	24.24%	53	40.15%	5	3.79%
3	Urogenital disorders	2	1.52%	14	10.61%	22	16.67%	49	37.12%	4	3.03%
4	Cardio-vascular symptoms	1	0.76%	6	4.55%	21	15.91%	44	33.33%	4	3.03%
5	Sleep dysfunction	3	2.27%	9	6.82%	26	19.70%	44	33.33%	5	3.79%
6	Fatigue	2	1.52%	11	8.33%	20	15.15%	40	30.30%	5	3.79%
7	Apathy	1	0.76%	5	3.79%	22	16.67%	22	16.67%	3	2.27%
8	Skin symptoms	1	0.76%	5	3.79%	12	9.09%	17	12.88%	3	2.27%
9	neuropsychiatric symptoms	1	0.76%	8	6.06%	25	18.94%	39	29.55%	4	3.03%
10	respiratory dysfunction	0	0.00%	4	3.03%	5	3.79%	12	9.09%	6	4.55%
11	sexual dysfunction	1	0.76%	8	6.06%	17	12.88%	32	24.24%	3	2.27%
12	sensory dysfunction	1	0.76%	3	2.27%	18	13.64%	26	19.70%	5	3.79%
13	weight change	1	0.76%	8	6.06%	14	10.61%	20	15.15%	2	1.52%
14	depression	1	0.76%	12	9.09%	20	15.15%	33	25.00%	4	3.03%
15	cognitive decline	0	0.00%	15	11.36%	24	18.18%	53	40.15%	5	3.79%

Tabl. 5.5 Distribution of individual NMS by age

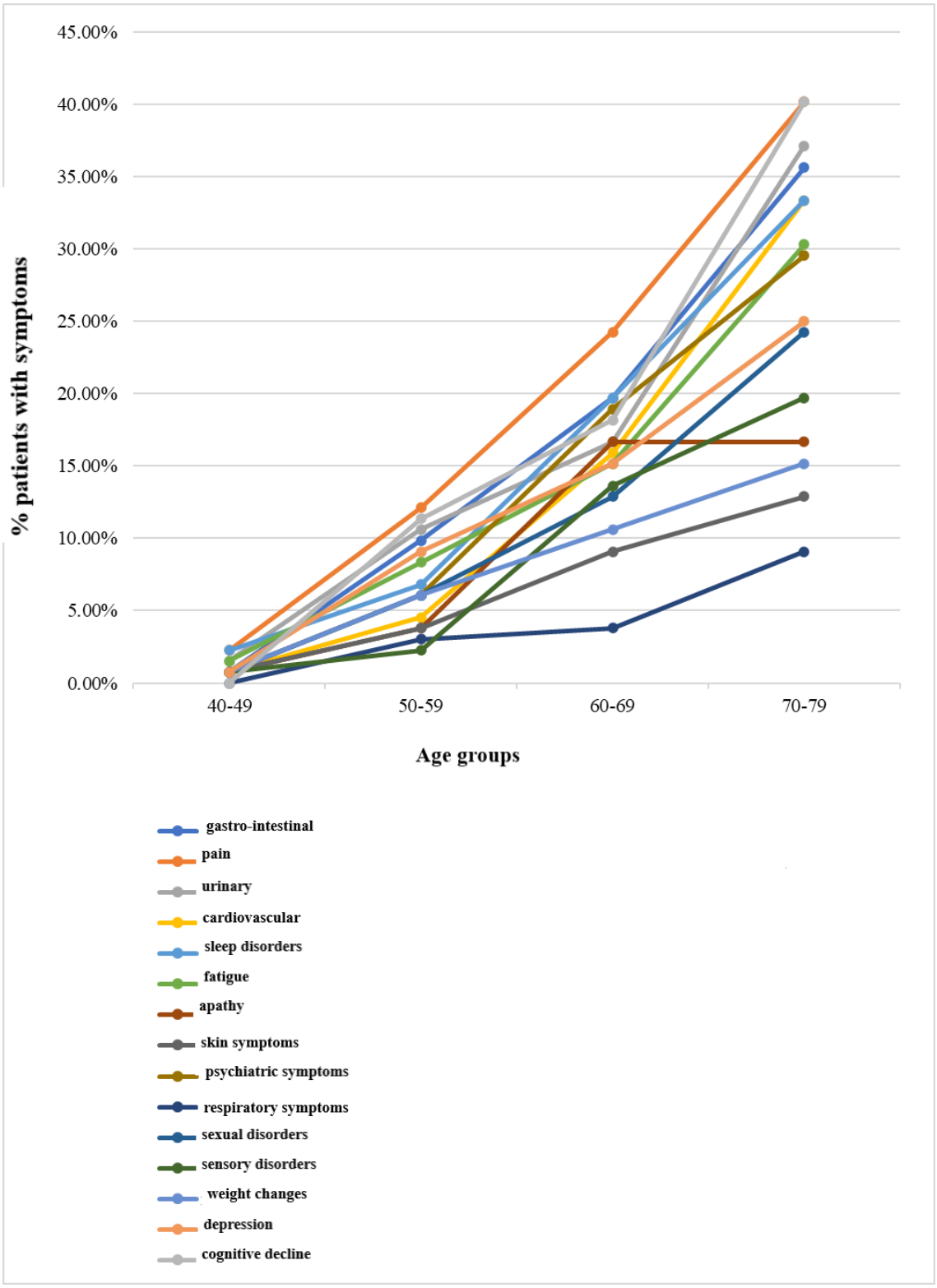

Fig. 5.5 Distribution of individual NMS by age

From the presented Table 5.5. it can be observed that the changes in the frequency of NMS according to age are dynamic and diverse, and will be examined separately for each NMS.

5.5.1. Distribution of Gastrointestinal NMS

The frequency of gastrointestinal NMS shows two peaks - in the 6th and 7th decades of life. There is no significant difference observed in the average age of patients in the studied groups: K-W=5.2302, p=0.0732.

GIT symptoms	Number	Median age	Age interval
Without GIT symptoms	42	67	48-86
With one GIT symptom	23	69	48-76
With two or more GIT symptoms	67	72	52-84

Tabl. 5.5.1. Frequence of GIT symptoms by age

5.5.2. Pain Symptoms

The frequency of pain gradually increases and reaches its highest peak in the 7th decade - 53.23%. No difference in age is observed among groups of patients who report or do not report the presence of pain symptoms: K-W=0.6100, p=0.4348.

Pain	Number of patients	Median age	Age interval
With pain	23	69	57 - 84
Without pain	109	70	48 - 86

Table 5.5.2. Distribution of patients based on the presence of pain symptoms

5.5.3. Urogenital Symptoms

Although urinary symptoms were more frequently observed in patients over 60 years old, reaching their peak (58.24%) after the age of 70, there is no statistically significant difference in age among patients with urinary system disorders: K-W=3.1521, p=0.0758.

Urogenital disoreders	Number of patients	Median age	Age interval
Without	41	67	48 - 84
With	91	71	48 - 86

Table 5.5.3. Distribution of patients based on the presence of urogenital symptoms

5.5.4. Cardiovascular disorders (CVD)

Cardiovascular disorders are more common after the 5th decade (27.63%) and increase to 63.16% after 70 years. A significant difference in age is observed in patients with cardiovascular system disorders. Older patients more often have cardiovascular symptoms: K-W=11.5492, p=0.0007.

CVD	Number of patients	Median age	Age interval
Without	56	66	48 - 84
With	76	72	48 - 86

Table 6.5.4. Distribution of patients based on the presence of cardiovascular symptoms

5.5.5. Sleep Disturbances

Sleep disturbances are more characteristic after the age of 60 and reach 56.32% in the oldest age group. No relationship between age and sleep disorders is observed: K-W=3.7727, p=0.0521.

Sleep disturbances	Number of patients	Median age	Age interval
Without	45	67	52-84
With	47	71	48-86

Table 5.5.5. Distribution of patients based on the presence of sleep disturbances.

5.5.6. Fatigue

Fatigue is under 3% in patients up to 50 years old, but it increases with age and reaches 57.69% in patients over 70 years old. No relationship between age and the presence of fatigue is established: K-W=1.6904, p=0.1935.

Fatigue	Number of patients	Median age	Age interval
Without	54	67.5	49 - 84
With	78	71	48 - 86

Table 5.5.6. Distribution of patients based on data on increased fatigue.

5.5.7. Apathy

In patients up to 50 years old, apathy is under 2.0%; with advancing age, it increases to 47.17%. No relationship between age and the presence of apathy is observed: K-W=0.3243, p=0.5690.

Apathy	Number of patients	Median age	Age interval
Without	79	70	48 - 86
With	53	69	48-84

Table 5.5.7. Distribution of patients based on the presence of apathy.

5.5.8. Skin Symptoms

Skin symptoms are relatively rare until the age of 60 (13.16%), but reach 52.63% at the end of the study age range. No relationship between age and the presence of skin symptoms is established: K-W=0.0276, p=0.8681.

Skin symptoms	Number of patients	Median age	Age interval
Without	94	70	48 - 86
With	24	71	49 - 84

Table 5.5.8. Distribution of patients based on the presence of skin symptoms.

5.5.9. Neuropsychiatric Symptoms

Psychiatric symptoms are around 1% of the NMS in patients up to 50 years of age but reach 55.84% in the oldest age group. A significant difference in age is observed in patients with psychiatric manifestations compared to those without: K-W=4.0993, p=0.0428.

Neuropsychiatric symptoms	Number of patients	Median age	Age interval
Without	55	67	48 - 86
With	77	71	49 - 84

Table 5.5.9. Distribution of patients based on the presence of neuropsychiatric symptoms.

5.5.10. Respiratory Symptoms

Respiratory symptoms show a gradual increase from 14.81% in the 5th decade to 66.67% after 70 years. A significant difference in age is observed in patients with respiratory system disorders compared to those without: K-W=6.1517, p=0.031. Older patients more often have respiratory symptoms.

Respiratory symptoms	Number of patients	Median age	Age interval
Without	105	69	48 - 79
With	27	74	57 -86

Table 5.5.10. Distribution of patients based on the presence of respiratory symptoms.

5.5.11. Sexual Disorders

In patients up to 50 years of age, sexual symptoms are below 2% and gradually increase to 57.38% after 70 years. A significant difference in age is observed in patients with sexual dysfunction compared to those without: K-W=8.3285, p=0.0039.

Sexual Disorders	Number of patients	Median age	Age interval
Without	74	67	49 - 84
With	58	72	48 - 86

Table 5.5.11. Distribution of patients based on the presence of sexual disorders.

5.5.12. Sensory Disorders

Sensory symptoms are more characteristic after the age of 60 (38.96%) and increase to 58.49% at the end of the study age range. A significant difference in age is observed in patients with sensory disorders compared to those without: K-W=4.8970, p=0.0269.

Sensory disorders	Number of patients	Median age	Age interval
Without	79	68	48 - 84
With	54	72	49 - 86

Table 5.5.12. Distribution of patients based on the presence of sensory disorders.

5.5.13. Weight Change

Weight change (reduction) shows a gradual increase from the 5th decade (17.78%) to 48.89% in the oldest age group. No significant difference in age is observed in patients with weight changes compared to those without: K-W=0.5446, p=0.4605.

Weight Change	Number of patients	Median age	Age interval
Without	87	70	48 - 86
With	45	69	48 - 84

Table 5.5.13. Distribution of patients based on reported weight changes.

5.5.14. Depression

Symptoms of depression are below 2% in patients up to 50 years of age and gradually increase to ~53% in the oldest age group. The distribution by age and the presence and severity of depressive changes do not show the presence of statistically significant differences: K-W=3.6592, p=0.3007.

Depression	Number of patients	Median age	Age interval
Absent	62	69.5	48 - 86
Mild	55	70	48 - 78
Moderate	10	72,5	56 - 84
Severe	5	64	57 - 84

Table 5.5.14. Distribution of patients based on the presence of depression.

5.5.15. Cognitive Disorders

Up until the age of 50, no cognitive disorders are registered; in the following decades, they increase to ~60% in the oldest age group. The distribution by age and the presence of cognitive disorders show no statistically significant differences: K-W=12.576, p=0.0056.

Cognitive disorders	Number of patients	Median age	Age interval
Absent	35	66	48 - 80
Mild	89	71	52 - 86
Moderate	6	69.5	57 - 82
Severe	2	77	75 - 79

Table 5.5.15. Distribution of patients based on the presence of cognitive disorders.

5.5.16. Summary

Age, as well as gender, are of significant importance in neurodegenerative diseases, especially in Parkinson's disease (PD). Several studies have focused on the influence of age in PD. The data on the influence of age in PD with non-motor symptoms (NMS) are inconsistent and varied. Older patients tend to have a higher number and more severe NMS. Patients with earlier onset are characterized by depression (more than 40%), isolation from family life, and feelings of guilt and inadequacy. Spica V et al. (2013) also found a predominance of more NMS in patients with earlier onset of the disease. Virameteekul S et al. (2021) found that older patients more frequently experience gastrointestinal and urinary problems, fatigue, sleep disturbances, and dementia, while those at an earlier age experience depression, anxiety, and sexual problems.

In other studies, such correlation with age is not established. Ou R et al. (2014) found, in a study of four groups of PD patients (<50 to 70> years), that age does not influence the frequency and manifestation of NMS; the frequency and manifestation of NMS progress as the disease advances. Sánchez-Martínez CM

et al. (2019) also did not find a correlation between the frequency of NMS and age, but rather with the duration of the disease. Patients with a disease duration of more than 10 years have a higher frequency of NMS. Almost all patients experience one or more NMS during the course of the disease.

In our study, some significant differences in the prevalence of several NMS were identified according to age. Patients with a higher mean age of 72 years (48-86) more frequently have **cardiovascular disorders**: K-W=11.5492, p=0.0007. Such a difference, again at a mean age of 72 years (48-86), is also observed for **neuropsychiatric symptoms**—they are more common in the older age group: K-W=4.0993, p=0.0428. Significant differences were also found in other NMS, again with a predominance of NMS in older patients:

- Respiratory symptoms: mean age 74 years (57-86): K-W=6.1517, p=0.031
- Sexual dysfunction: mean age 72 years (48-86): K-W=8.3285, p=0.0039
- Sensory disorders: mean age 72 years (49-86): K-W =4.8970, p=0.0269

The age characteristics in our study differ regarding the mentioned NMS, but there is also a significant difference in the literature regarding the frequency of individual NMS by age.

5.6. Distribution of NMS According to Disease Stage

	Stage							
Symptom	1	%	2	%	3	%	4	%
gastro-intestinal	12	9.09%	37	28.03%	29	21.97%	12	9.09%
pain	22	16.67%	44	33.33%	35	26.52%	8	6.06%
urinary disorders	15	11.36%	34	25.76%	31	23.48%	11	8.33%
cardiovascular symptoms	10	7.58%	31	23.48%	27	20.45%	8	6.06%
sleep disorders	10	7.58%	36	27.27%	29	21.97%	12	9.09%
fatigue	17	12.88%	26	19.70%	25	18.94%	10	7.58%
apathy	11	8.33%	21	15.91%	12	9.09%	9	6.82%
skin symptoms	3	2.27%	13	9.85%	14	10.61%	8	6.06%
psychiatric disorders	8	6.06%	32	24.24%	27	20.45%	10	7.58%
respiratory disorders	2	1.52%	10	7.58%	14	10.61%	1	0.76%
sexual disorders	15	11.36%	19	14.39%	20	15.15%	7	5.30%
sensory disorders	4	3.03%	25	18.94%	19	14.39%	5	3.79%
weight changes	9	6.82%	22	16.67%	11	8.33%	3	2.27%
depression	18	13.64%	19	14.39%	24	18.18%	9	6.82%
cognitive decline	18	13.64%	32	24.24%	35	26.52%	12	9.09%

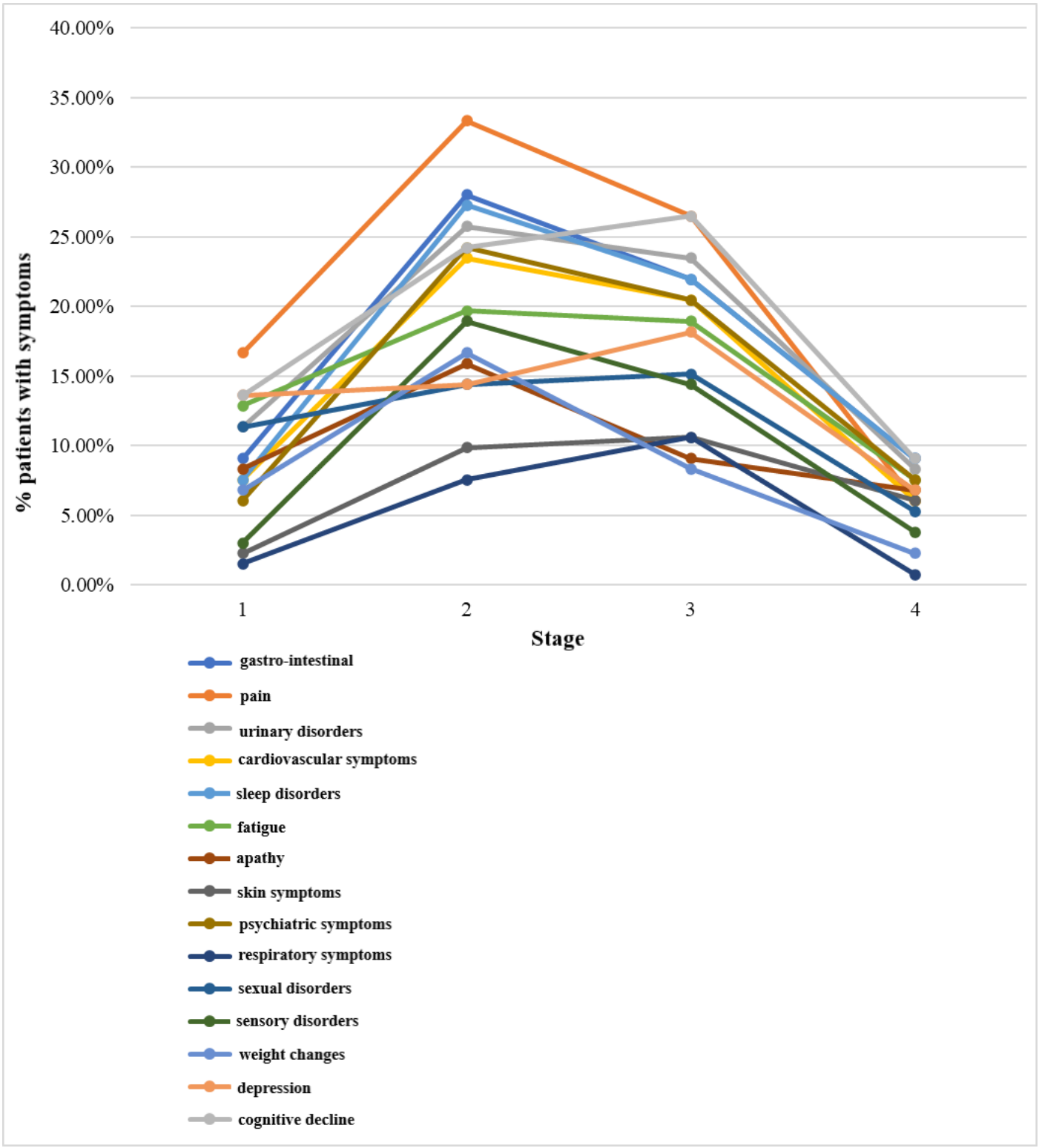

Fig. 5.6 General distribution of NMS according to disease stage

Changes in the frequency of NMS according to stage are dynamic and vary for individual symptoms.

5.6.1. Gastrointestinal Symptoms

Ninety patients (68.18%) present with symptoms. There is a significant relationship between disease stage and gastrointestinal symptoms, chi-square=10.05, Df=3, p=0.0182. In the second and third stages, patients with gastrointestinal symptoms dominate; in the fourth stage, all patients exhibit gastrointestinal symptoms.

Stage	Without symptoms	With symptoms
First	12 (09.09%)	11 (8.33%)
Second	17 (12.88%)	37 (28.03%)
Third	13 (9.85%)	30 (28.73%)
Forth	0 (0.00%)	12 (09.09%)

Tabl. 5.6.1. Frequency of GIT symptoms according to stage

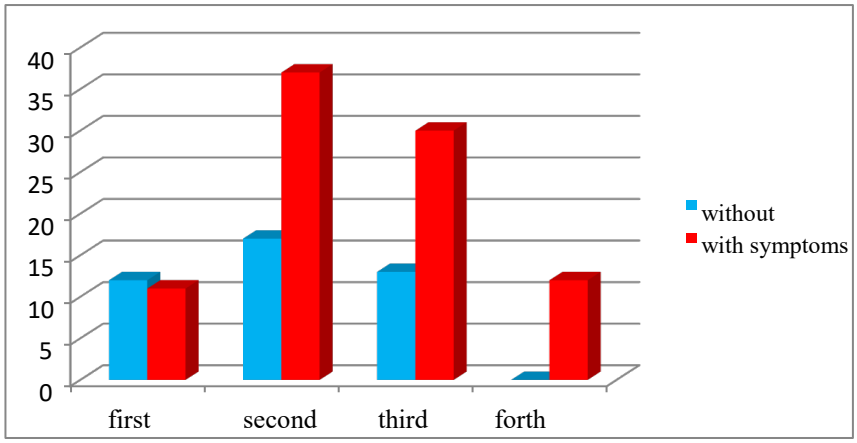

Fig.5.6.1. Frequency of GIT symptoms according to stage

5.6.2. Pain Symptoms

The presence of pain symptoms and their distribution by stage does not show a statistically significant relationship between the studied categories: chi-square=3.41, Df=3, p=0.3322. Pain symptoms are present in 109 cases (82.58%). Pain symptoms occur in all stages of the disease without dominating in a specific stage.

Stage	Without symptoms	With symptoms
First	2 (1.52%)	21 (15.91%)
Second	10 (7.58%)	44 (33.33%)
Third	7 (5.30%)	36 (27.27%)
Forth	4 (3.03%)	8 (6.06%)

Tabl. 5.6.2. Frequency of pain according to stage

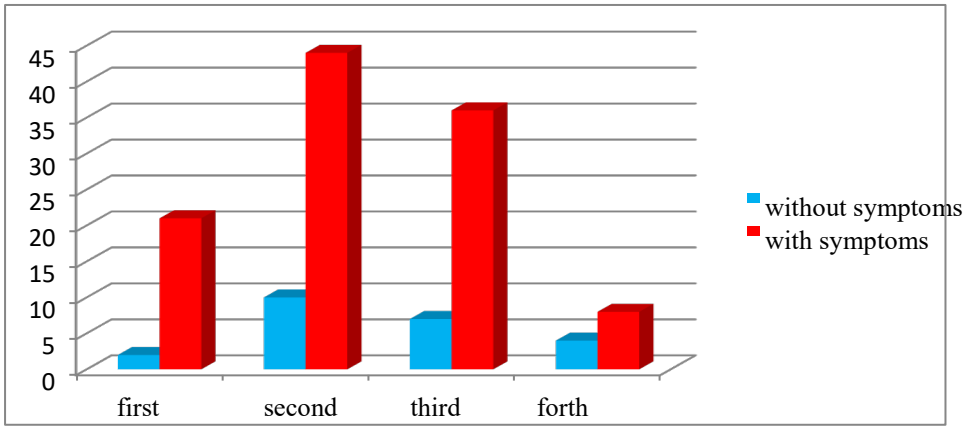

Fig. 5.6.2. Frequency of pain according to stage

5.6.3. Urogenital Disorders

There is no correlation between the distribution of cases by stage and the presence of symptoms from the urogenital system: chi-square=6.36, Df=3, p=0.0952. Ninety-one cases (68.94%) present urogenital disturbances. There is a tendency for them to occur more frequently in the third and fourth stages of the disease.

Stage	Without symptoms	With symptoms
First	9 (6.82%)	14 (10.61%)
Second	21 (15.91%)	33 (25.00%)
Third	10 (7.58%)	33 (25.00%)
Forth	1 (0.76%)	11 (8.33%)

Tabl. 5.6.3. Frequency of urogenital symptoms in different stages of PD.

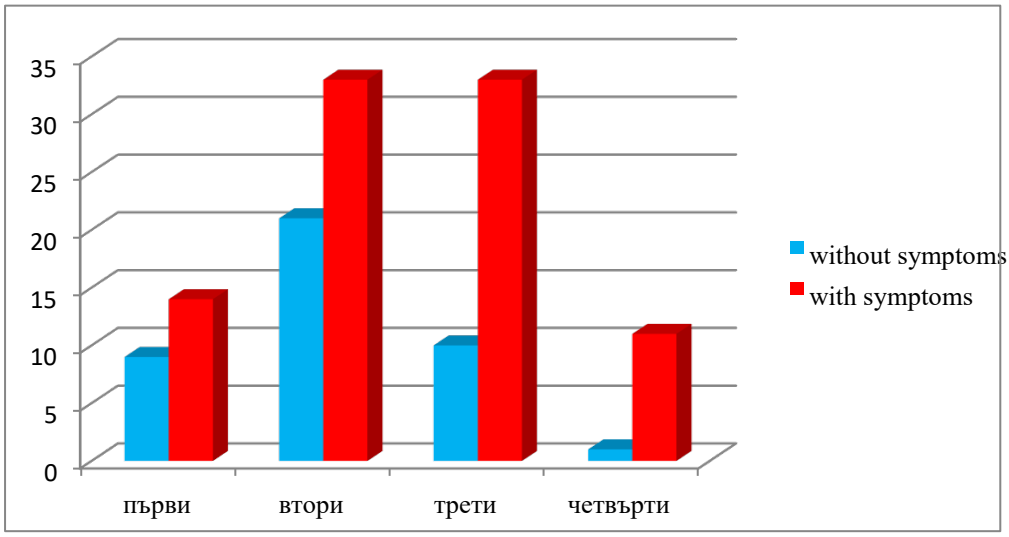

Fig.5.6.3. Frequency of urogenital symptoms in different stages of PD.

5.6.4. Cardiovascular Symptoms

There is no correlation between the distribution of cases by stage and the presence of cardiovascular symptoms: chi-square=2.76, Df=3, p=0.4307. Seventy-six cases (57.58%) present concomitant cardiovascular diseases. They occur more frequently (but not statistically significantly) in the second, third, and fourth stages of the disease.

Stage	Without symptoms	With symptoms
First	13 (9.85%)	10 (7.58%)
Second	23 (17.42%)	31 (23.48%)
Third	16 (12.12%)	27 (20.45%)
Forth	4 (3.03%)	8 (6.06%)

Tabl.5.6.4. Frequency of cardiovascular symptoms according to stage

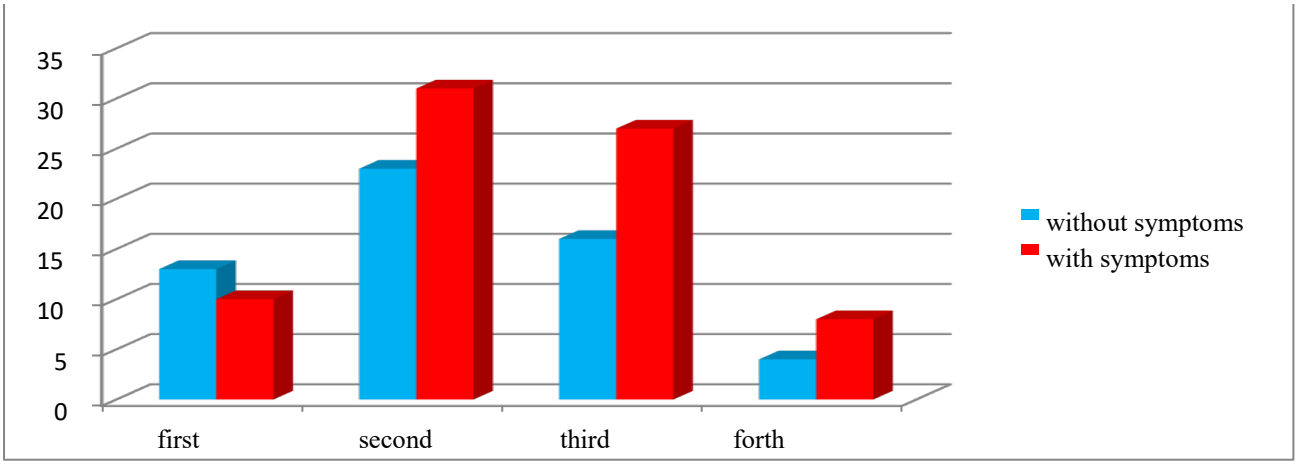

Fig.5.6.4. Frequency of cardiovascular symptoms according to stage

5.6.5. Sleep Disturbances

A significant relationship is observed between disease stage and sleep disturbances: chi-square=13.85, Df=3, p=0.0031. Eighty-seven cases (65.91%) have sleep disturbances. Symptoms related to sleep occur more frequently in patients at advanced stages of the disease, with all studied patients in the fourth stage having symptoms related to sleep disturbances.

Stage	Without symptoms	With symptoms
First	14 (10.61%)	9 (6.82%)
Second	18 (13.64%)	36 (27.27%)
Third	13 (9.85%)	30 (22.73%)
Forth	0 (0.00%)	12 (9.09%)

Tabl. 5.6.5. Frequency of sleep disturbances according to stage

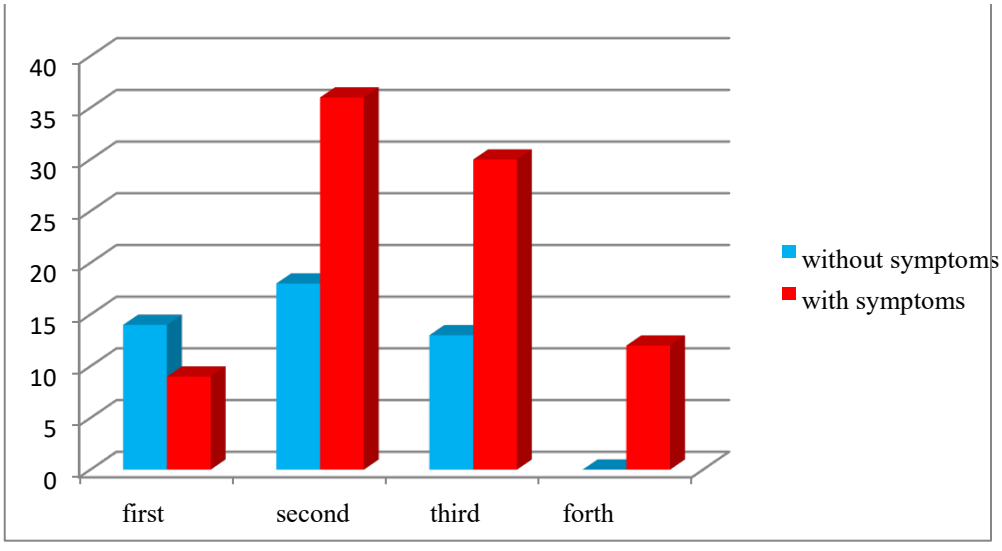

Fig. 5.6.5. Frequency of sleep disturbances according to stage

5.6.6. Fatigue

There is no observed relationship between stage and the presence of fatigue among the studied patients: chi-square=6.19, Df=3, p=0.1026. Fatigue is present in 78 cases (59.09%) and occurs as a symptom in all stages of the disease.

Stage	Without symptoms	With symptoms
First	8 (6.06%)	15 (11.36%)
Second	28 (21.21%)	26 (19.70%)
Third	16 (12.12%)	27 (20.45%)
Forth	2 (1.52%)	10 (7.58%)

Tabl. 5.6.6. Frequence of fatigue complaints according to stage

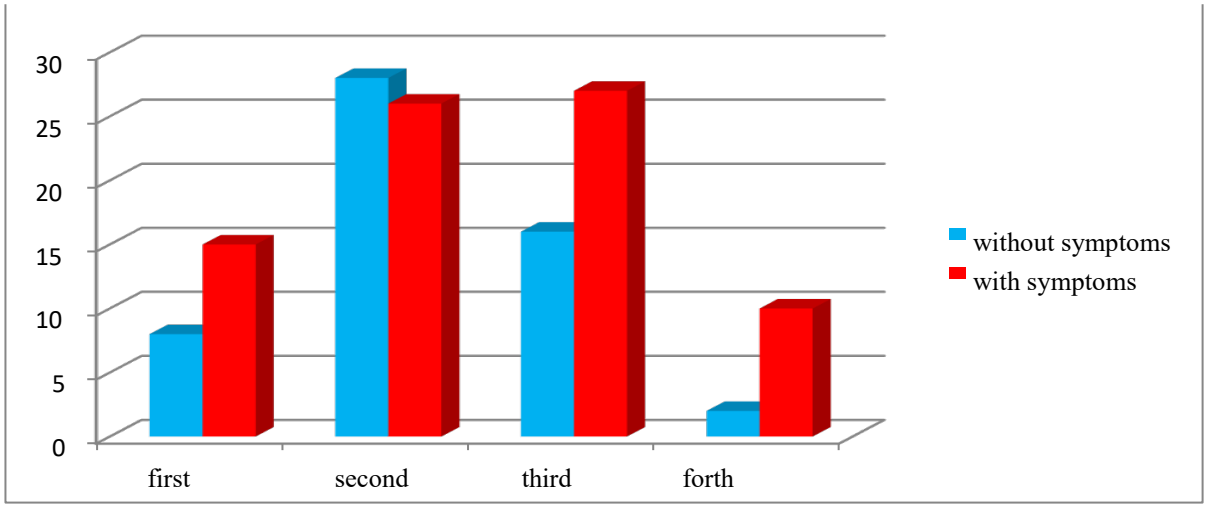

Fig. 5.6.6. Frequence of fatigue complaints according to stage

5.6.7. Apathy

A significant relationship is observed between disease stage and manifestations of apathy: chi-square=8.61, Df=3, p=0.0350. Apathy is present in 53 cases (40.15%), with its highest frequency in the fourth stage of the disease (in 9 out of 12 cases).

Stage	Without symptoms	With symptoms
First	12 (9.09%)	11 (8.33%)
Second	34 (25.76%)	20 (15.15%)
Third	30 (22.73%)	13 (9.85%)
Forth	3 (2.27%)	9 (6.82%)

Tabl. 5.6.7. Frequency of apathy according to stage

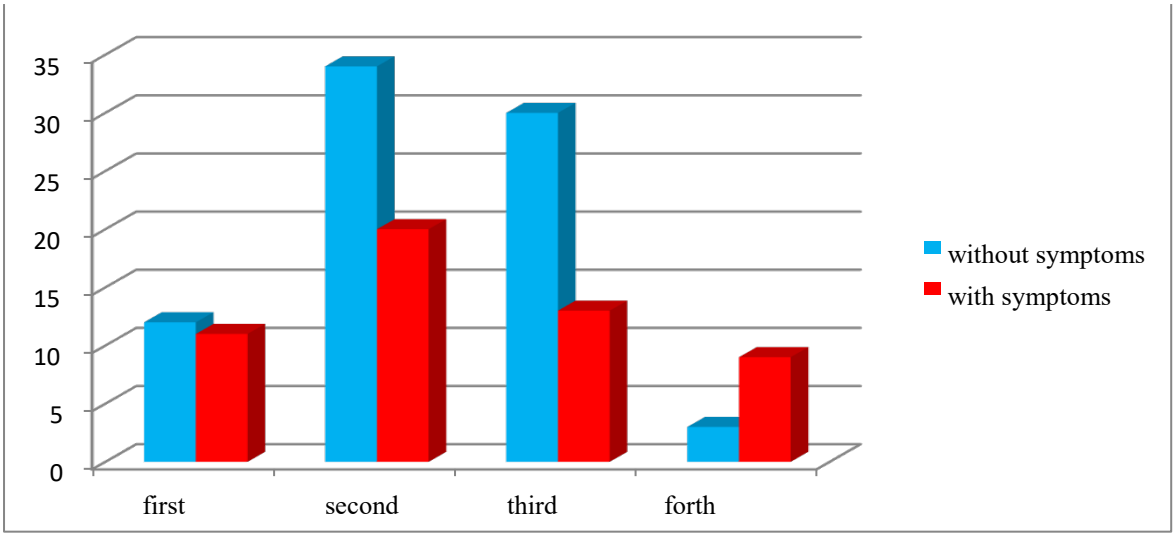

Fig. 5.6.7. Frequency of apathy according to stage

5.6.8. Skin Symptoms

There is a relationship between disease stage and the presence of seborrhea and/or hyperhidrosis among the studied patients: chi-square=12.06, Df=3, p=0.0072. Thirty-eight cases (28.79%) present skin symptoms. As the disease progresses (stage), symptoms become more frequent among the studied patients.

Stage	Without symptoms	With symptoms
First	20(15.15%)	3 (2.27%)
Second	41(31.06%)	13(9.85%)
Third	29(21.97%)	14(10.61%)
Forth	4(3.03%)	8(6.06%)

Tabl. 5.6.8. Frequency of skin symptoms according to stage

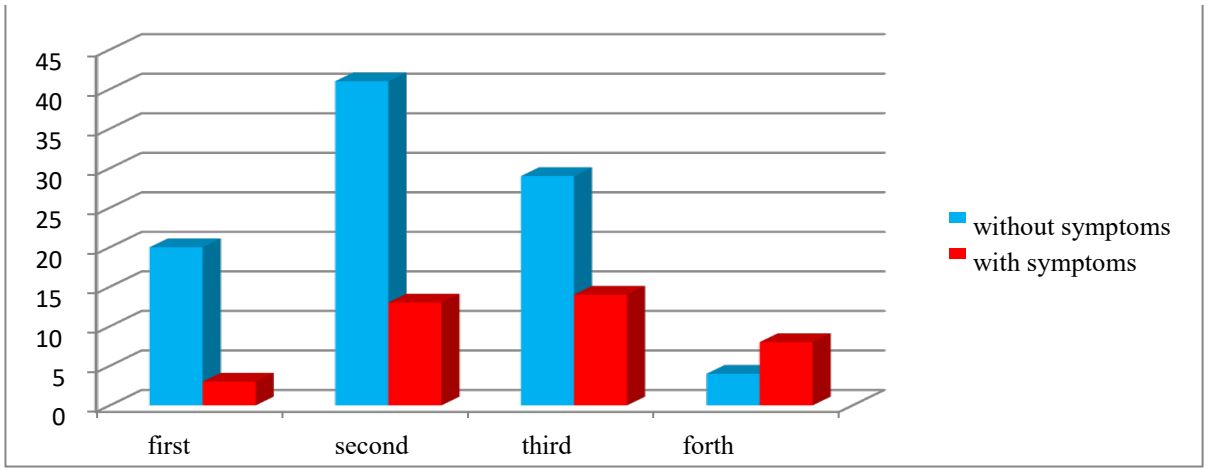

Fig.5.6.8. Frequency of skin symptoms according to stage

5.6.9. Psychiatric Manifestations

A dependency is observed between disease stage and the presence of psychiatric manifestations among the studied patients: chi-square=8.70, Df=3, p=0.0335. Seventy-seven cases (58.33%) exhibit psychiatric manifestations, significantly more frequently in advanced stages of the disease.

Stage	Without symptoms	With symptoms
First	15 (11.36%)	8 (6.06%)
Second	22 (16.67%)	32 (24.24%)
Third	16 (12.12%)	27 (20.45%)
Forth	2 (1.52%)	10 (7.58%)

Tabl. 5.6.9. Frequency of psychiatric symptoms according to stage

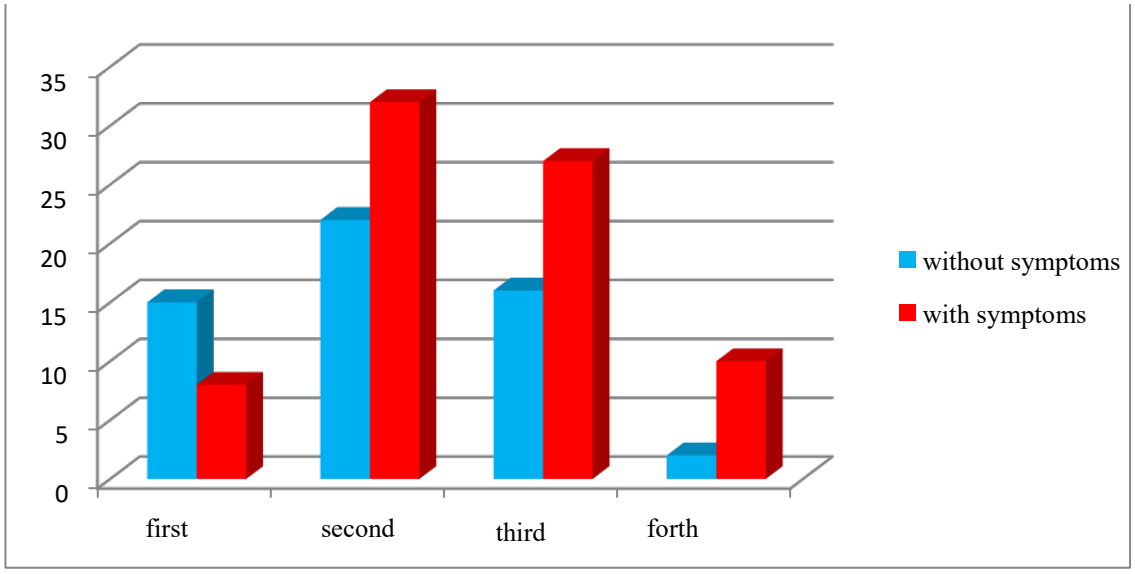

Fig. 5.6.9. Frequency of psychiatric symptoms according to stage

5.6.10. Respiratory Changes

There is no significant correlation between the distribution by stage and the presence of respiratory symptoms: chi-square=7.03; Df=3; p=0.0708. Respiratory problems are present in 27 cases (20.45%) of the studied cases.

Stage	Without symptoms	With symptoms
First	21(15.91%)	2(1.52%)
Second	44(33.33%)	10(7.58%)
Third	29(21.97%)	14(10.61%)
Forth	11(8.33%)	1(0.76%)

Tabl. 5.6.10. Frequency of respiratory symptoms according to stage

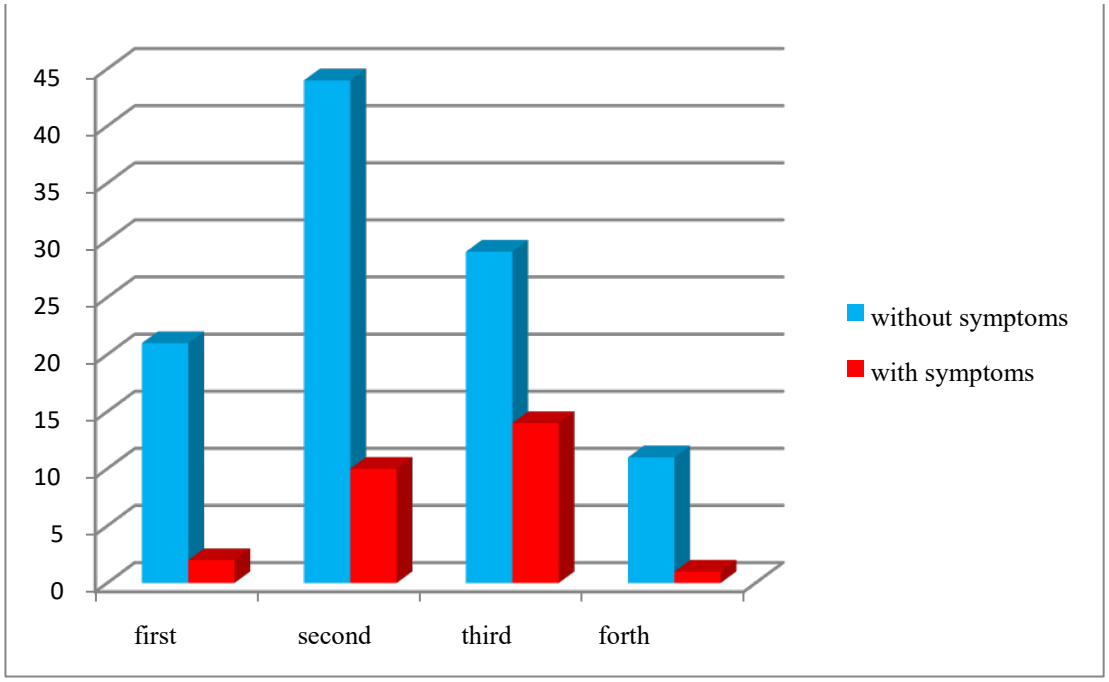

Fig.5.6.10. Frequency of respiratory symptoms according to stage

5.6.11. Sexual Dysfunctions

There is no statistically significant difference in the presence of sexual dysfunctions distributed by disease stage: chi-square=4.76, Df=3, p=0.1904. Sexual dysfunction is present in 61 cases (46.21%) of the studied cases.

Stage	Without symptoms	With symptoms
First	10(7.58%)	13(9.85%)
Second	35(26.52%)	19(14.39%)
Third	21(15.91%)	22(16.67%)
Forth	5(3.79%)	7(5.30%)

Tabl. 5.6.11. Frequency of sexual dysfunction according to stage

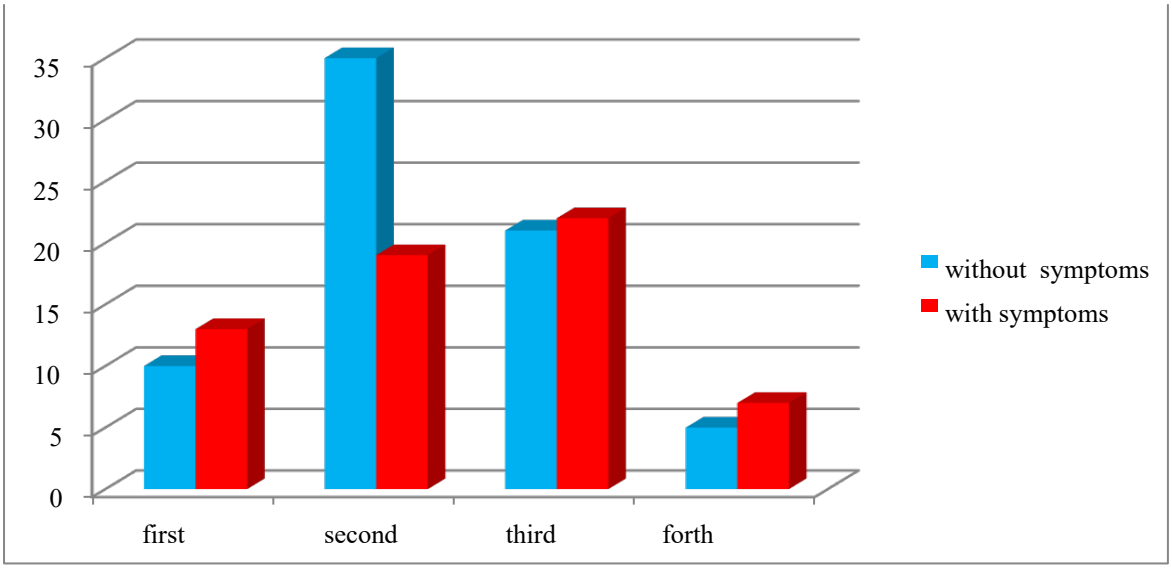

Fig.5.6.11. Frequency of sexual dysfunction according to stage

5.6.12. Sensory Disorders

There is no significant relationship between the distribution by disease stage and the presence of sensory disorders: chi-square=3.96; Df=3; p=0.2656. Sensory disorders are present in 53 cases (40.15%) of the studied cases.

Stage	Without symptoms	With symptoms
First	18(13.64%)	5(3.79%)
Second	30(22.73%)	24(18.18%)
Third	24(18.18%)	19(14.39%)
Forth	7(5.30%)	5(3.79%)

Tabl. 5.6.12. Frequency of sensory disorders according to stage

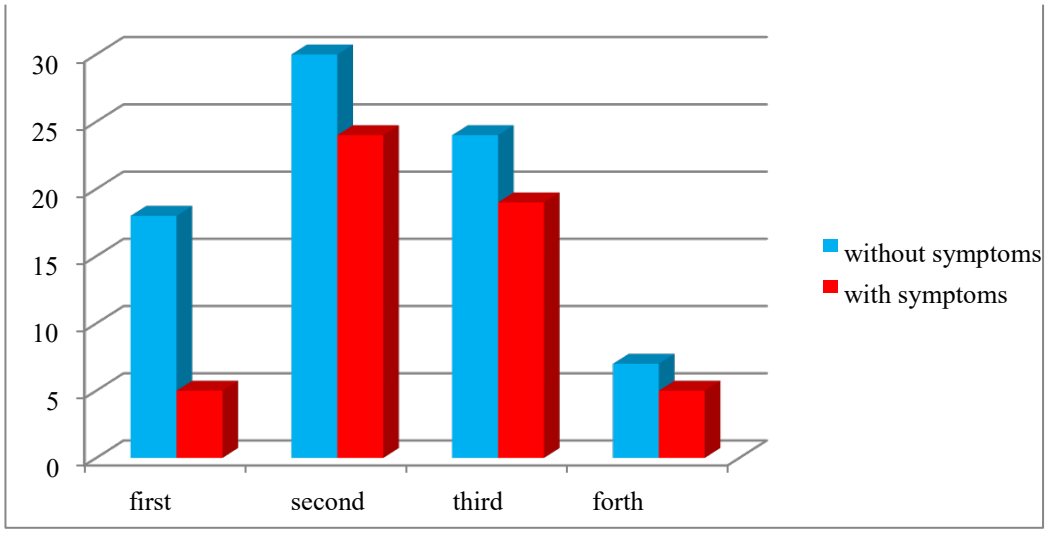

Fig. 5.6.12. Frequency of sensory disorders according to stage

5.6.13. Weight Changes

There is no significant relationship between the distribution by stage and the presence of changes in body weight: chi-square=2.24; Df=3; p=0.5239. Weight reduction is present in 45 cases (34.09%) of the studied cases.

Stage	Without symptoms	With symptoms
First	15 (11.36%)	8 (6.06%)
Second	32 (24.24%)	22 (16.67%)
Third	31 (23.48%)	12 (9.09%)
Forth	9 (6.82%)	3 (2.27%)

Tabl. 5.6.13. Frequency of weight change cases according to stage

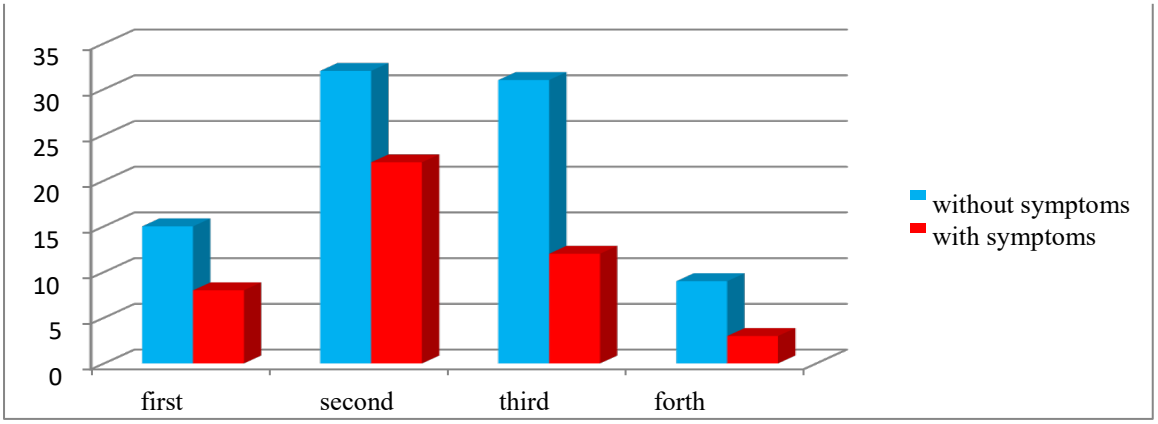

Fig.5.6.13. Frequency of weight change cases according to stage

5.6.14. Depression

A dependency is observed between disease stage and the presence of depressive changes among the studied patients: chi-square=13.71, Df=3, p=0.0033. Depression occurs in 70 patients (50.0%), being more common in the 3rd and 4th stages of the disease.

Stage	Without symptoms	With symptoms
First	6(4.55%)	17(12.88%)
Second	35(26.52%)	19(14.39%)
Third	18(13.64%)	25(18.94%)
Forth	3(2.27%)	9(6.82%)

Tabl. 5.6.14. Frequency of depression according to stage

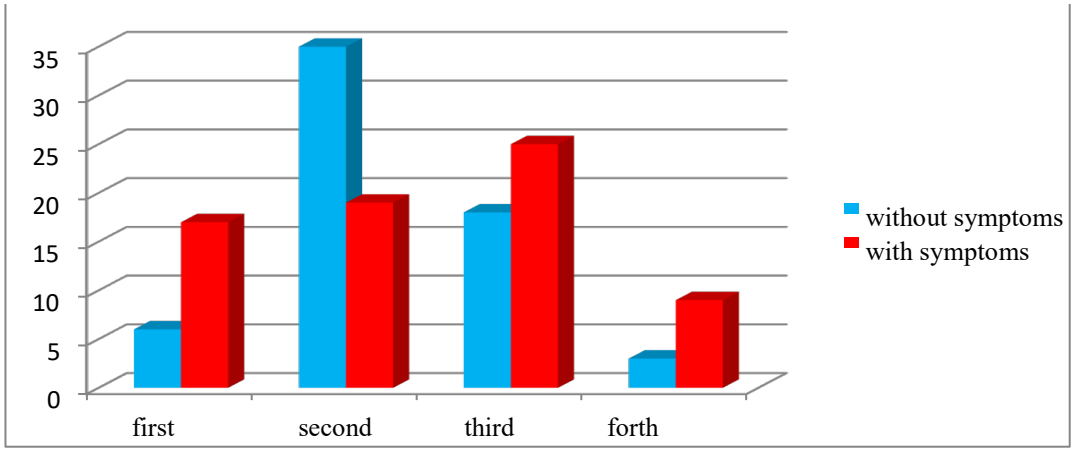

Fig. 5.6.14. Frequency of depression according to stage

5.6.15. Cognitive Impairments

A dependency is observed between disease stage and the presence of cognitive impairments among the studied patients: chi-square=12.25, Df=3, p=0.0066.

Stage	Without symptoms	With symptoms
First	6 (4.55%)	17 (12.88%)
Second	22 (16.67%)	32 (24.24%)
Third	7 (5.30%)	36 (27.27%)
Forth	0 (0.00%)	12 (9.09%)

Tabl. 5.6.15. Frequency of cognitive impairments according to stage

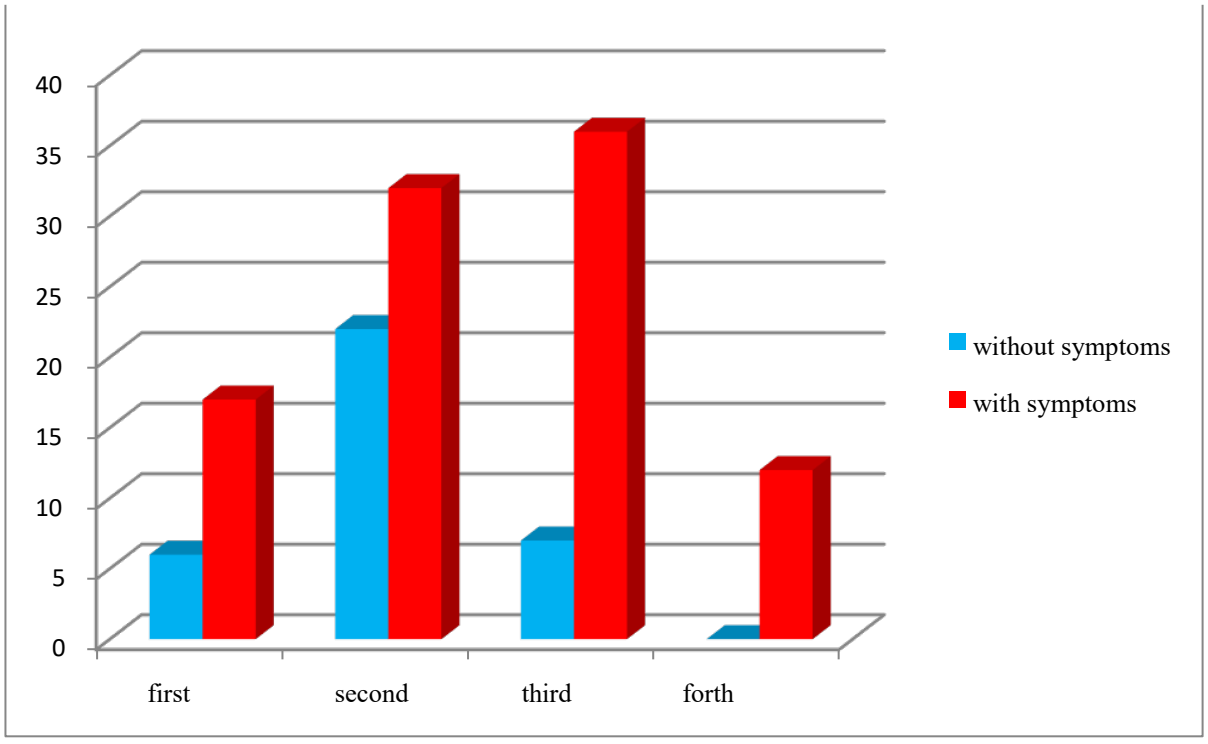

Fig.5.6.15. Frequency of cognitive impairments according to stage

Cognitive impairments are present in 97 patients (73.48%), with higher prevalence in the 3rd and 4th stages of the disease.

5.6.16. Distribution by Presence of Non-Motor Symptoms

A dependency is observed between disease stage and the presence of non-motor symptoms (up to 3; between 4 and 9, and 10 or more symptoms): chi-square=24.13, Df=6, p=0.0005. (here, the dependency is not reliable due to the many positions with <5 cases).

Stage	up to 3 symptoms	between 4 and 9 symptoms	10 and more symptoms
First	3 (2.27%)	3 (2.27%)	17 (12.88%)
Second	3 (2.27%)	12 (9.09%)	39 (29.55%)
Third	4 (3.03%)	18 (13.64%)	21 (15.91%)
Forth	0 (0.00%)	10 (7.58%)	2 (1.52%)

Tabl. 5.6.16. Distribution of cases by number of NMS and disease stage

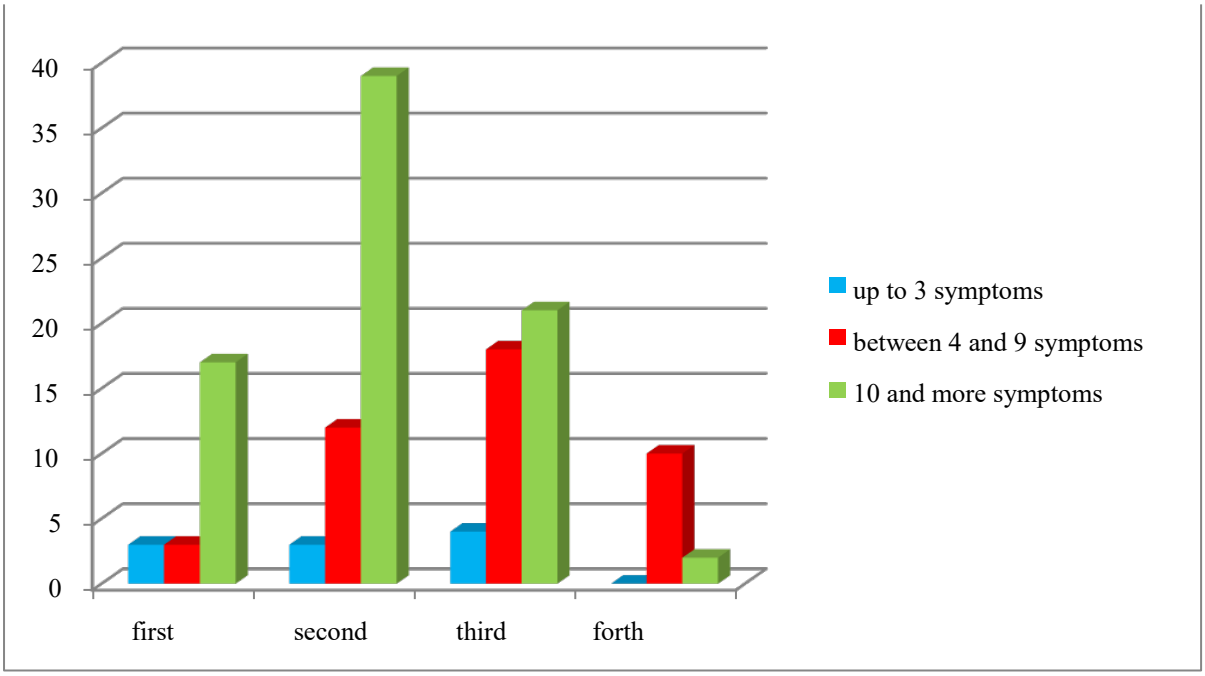

Fig.5.6.16. Distribution of cases by number of NMS and disease stage

In the 4th stage of the disease, there are no patients with up to three non-motor symptoms.

5.6.17. Summary

When studying the relationship between disease stage and non-motor symptoms (NMS), an increase in the number and frequency of NMS is observed with disease progression. In the first, second, and third stages, cases with 4 to 9 symptoms predominate, while in the fourth stage, there are no cases with up to three symptoms. Significant differences according to disease stage and the frequency and number of NMS are observed for the following symptoms: gastrointestinal symptoms, sleep disturbances, apathy, skin

symptoms, psychiatric symptoms, depression, and cognitive impairments. Literature data on the relationship between disease stage and NMS frequency are inconsistent. Some studies find no significance in disease stage severity. Zis P. et al. (2015) identify NMS in untreated and early-stage patients.

Other studies find a correlation between disease stage and NMS frequency and severitySánchez-Martínez C. et al. (2019) note significant frequency and severity of gastrointestinal, urinary, cardiovascular, and sexual symptoms in stages 4-5. Similar findings are supported by Ou R. et al. (2015), where NMS severity depends only on disease progression, with age having no significance.

5.7. Findings

1. All patients have at least one NMS.
2. Patients with a greater number of NMS - 9 or more - prevail, and this is observed in both genders, with no statistically significant difference.
3. A greater number of NMS is detected in older patients (K-W=15.337, p=0.0005).
4. A significant relationship is observed between gender distribution and the presence of cardiovascular symptoms - they are more common in women ($\chi 2$=10.44, Df=1; p=0.0012).
5. Skin symptoms are more common in men (21.97% compared to 6.82%) ($\chi 2$=7.77, Df=1, p=0.0053).
6. Older patients more frequently experience cardiovascular symptoms (K-W=11.5492, p=0.0007).
7. Respiratory symptoms are more common in older patients (K-W=6.1517, p=0.031).

6. Conclusions

• The questionnaire introduced and used in Bulgarian language is convenient for obtaining adequate results in researching NMS in PD.

• The frequency of NMS is high - all patients have at least one symptom.

• Patients with a higher number of NMS - 9 or more - prevail in both genders, with no statistically significant difference.

• A higher number of NMS is observed in older patients (statistically significant difference - KW=15.337, p=0.0005).

• The most common NMS in men are: pain - 81.08%; urogenital symptoms - 74.32%; gastrointestinal symptoms - 72.97%; cognitive impairments - 71.62%; and sleep disturbances - 68.91%.

• For women, pain is also the most common - 84.48%, followed by gastrointestinal symptoms - 79.10%; cognitive impairments - 75.86%; cardiovascular symptoms - 74.13%; and sleep and urogenital symptoms - each at 62.06%.

• Significant differences in the prevalence of NMS are observed according to age - patients with a higher average age of 72 years (range 48-86) more frequently experience cardiovascular diseases: K-W=11.5492, p=0.0007; nervous-psychological symptoms are more common in older age: K-W=4.0993, p=0.0428.

• Significant gender differences are observed in cardiovascular symptoms - cardiovascular symptoms prevail in women.

• Seborrhea and hyperhidrosis prevail in men.

7. Contributions

- For the first time in Bulgaria, a study on non-motor symptoms in patients with Parkinson's disease (PD) has been conducted.
- A Bulgarian version of the questionnaire for assessing non-motor symptoms in PD (NMS-PD) has been introduced.
- The frequency of symptoms has been investigated, revealing a high frequency of NMS-PD.
- The frequency of each non-motor symptom in patients with PD has been studied.
- The gender and age characteristics of patients have been studied in the context of individual non-motor symptoms.

8. Appendix:

Questionnaire card for disease stage (according to Hoehn and Yahr: 1; 1.5-2; 2.5-3; 4-5)

Questionnaire card for the Unified Parkinson's Disease Rating Scale part III (UPDRS-III)

Motor Examination.

18. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face". 2 = Slight but definitely abnormal diminution of facial expression

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

(head, upper and lower extremities)

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20. Tremor at rest

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands

0 = Absent

1 = Slight; present with action

2 = Moderate in amplitude, present with action

3 = Moderate in amplitude with posture holding as well as action

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent

1 = Slight or detectable only when activated by mirror or other movements

2 = Mild to moderate

3 = Marked, but full range of motion easily achieved

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal

1 = Mild slowing and/or reduction in amplitude

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)

0 = Normal

1 = Mild slowing and/or reduction in amplitude

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously).

0 = Normal

1 = Mild slowing and/or reduction in amplitude

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing

4= Can barely perform the task

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal

1 = Mild slowing and/or reduction in amplitude

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest).

0 = Normal.

1 = Slow, or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared).

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general).

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal.

Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, pover

Hamilton scale:

1 Depressed mood (sadness, hopeless, helpless, worthless)

0: Absent.

1: These feeling states indicated only on questioning.

2: These feeling states spontaneously reported verbally.

3: Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.

4: Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 Feelings of guilt

0: Absent.

1: Self reproach, feels he/she has let people down.

2: Ideas of guilt or rumination over past errors or sinful deeds.

3: Present illness is a punishment. Delusions of guilt.

4: Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 Suicide

0: Absent.

1: Feels life is not worth living.

2: Wishes he/she were dead or any thoughts of possible death to self.

3: Ideas or gestures of suicide.

4: Attempts at suicide (any serious attempt rate 4).

4 Insomnia: early in the night

0: No difficulty falling asleep.

1: Complains of occasional difficulty falling asleep, i.e. more than 1⁄2 hour.

2: Complains of nightly difficulty falling asleep.

5 Insomnia: middle of the night

0: No difficulty.

1: Patient complains of being restless and disturbed during the night.

2: Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 Insomnia: early hours of the morning

0: No difficulty.

1: Waking in early hours of the morning but goes back to sleep.

2: Unable to fall asleep again if he/she gets out of bed.

7 Work and activities

0: No difficulty.

1: Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.

2: Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).

3: Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.

4: Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 Retardation (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

0: Normal speech and thought.

1: Slight retardation during the interview.

2: Obvious retardation during the interview.

3: Interview difficult.

4: Complete stupor.

9 Agitation

0: None.

1: Fidgetiness.

2:Playing with hands, hair, etc.

3: Moving about, can't sit still.

4: Hand wringing, nail biting, hair-pulling, biting of lips.

10 Anxiety psychic

0: No difficulty.

1: Subjective tension and irritability.

2: Worrying about minor matters.

3: Apprehensive attitude apparent in face or speech.

4: Fears expressed without questioning.

11 Anxiety somatic (physiological concomitants of anxiety) such as: gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching cardio-vascular – palpitations, headaches respiratory – hyperventilation, sighing urinary frequency, sweating

0: Absent.

1: Mild.

2: Moderate.

3: Severe.

4: Incapacitating.

12 Somatic symptoms gastro-intestinal

0: None.

1: Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.

2: Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 General somatic symptoms

0: None.

1: Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.

2: Any clear-cut symptom rates 2.

14 Genital symptoms (symptoms such as loss of libido, menstrual disturbances)

0: Absent.

1: Mild.

2: Severe.

15 Hypochondriasis

0: Not present.

1: Self-absorption (bodily).

2: Preoccupation with health.

3: Frequent complaints, requests for help, etc.

4: Hypochondriacal delusions.

16 Loss of weight (rate either a or b)

a) According to the patient:

0: No weight loss.

1: Probable weight loss associated with present illness.

2: Definite (according to patient) loss.

3: Not assessed.

b) According to weekly measurements:

0: Less than 1 lb weight loss in week.

1: Greater than 1 lb weight loss in week.

2: Greater than 2 lb weight loss weight in week.

3: Not assessed.

17 Insight

0: Acknowledges being depressed and ill.

1: Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2: Denies being ill at all.

18 (not included in the assessment): Variation of symptoms throughout the day - whether they are worse in the morning or evening

0: No variation

1: Mild variation

2: Strong variation

19 (not included in the assessment): Derealization or depersonalization - feeling of unreality, as if everything is a movie, that the person is not themselves, but someone else, feeling detached from their body and seeing themselves from the outside, nihilistic ideas

0: Absent

1: Mild

2: Moderate

3: Severe

4: Disabling

20 (not included in the assessment): Paranoid (schizophrenic) symptoms

0: Absent

1: Suspicion towards oneself, others, society, government, conspiracies

2: Ideas of being watched, followed, interference in one's mind by external forces

3: False belief (delusion) of being watched, followed, persecuted

4: Hallucinations - auditory or visual about the above

21 (not included in the assessment): Obsessions - intrusive thoughts and compulsions that the patient struggles against

0: Absent

1: Mild

2: Severe

The result is interpreted as follows:

• 0-7: normal

• 8-13: mild depression

• 14-18: moderate depression

• 19-22: severe depression

• 23 or more: extremely severe depression

Questionnaire for the presence of NMS in patients with PD:

1. Gastrointestinal symptoms:

- Salivation: yes no
- Difficulty swallowing:
- Nausea/vomiting:
- Heartburn:
- Decreased bowel movements (<3 times per week):
- Incomplete bowel movements:
- Flatulence:

2. Pain:

- Indeterminate pain:
- Lower limb pain:
- Abdominal pain:
- Shoulder pain:

3. Symptoms of the urinary system:

- Frequent urination (every 2 hours):
- Urine leakage:
- Nocturia:
- Cardiovascular symptoms:

4. Cardiovascular symptoms:

- Dizziness in upright position:
- Fainting upon standing:

5. Sleep disturbances:

- (REM):
- Insomnia:
- Marked daytime sleepiness:
- Restless legs:

6. Fatigue:

- Fatigue during daily activities:

7. Apathy:

- Loss of interest in the surrounding environment:
- Loss of interest in daily activities:
- Awareness of deficit:

8. Memory impairments:

- Difficulty maintaining concentration:
- Short-term memory problems:
- Forgetting to perform daily activities:

9. Dermatological symptoms:

- Seborrhea:
- Hyperhidrosis:

10. Psychiatric symptoms:

- Anhedonia:
- Anxiety:
- Panic attack:
- Displays of aggression:
- Suicidal thoughts:
- Nervousness:
- Baseless fear:
- Sadness:
- Hallucinations:
- Delirium:

11. Respiratory symptoms:

    - Shortness of breath:
    - Cough:
    - Stridor:

12. Sensory disturbances:

    - Olfactory disturbances:
    - Diplopia:
    - Change in taste:

13. Weight change:

    - Weight loss:
    - Weight gain:

14. Sexual dysfunction:

    - Decreased libido:

15. Cognitive impairment:

    - Absent:
    - Mild:
    - Moderate:
    - Severe:

16. Depression:

    - Absent:
    - Mild:
    - Moderately expressed:
    - Severe:

Mini-Mental State Examination – MMSE

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

9. Publications related to the scientific work

9.1 Publications in Bulgarian or foreign publications indexed in SCOPUS and Web of Science:

- Marinova D., Danovska M., Todorova Y., Obreshkova T. Depression in Parkinson's disease – Profile and Assessment. Journal of Biomedical and Clinical research, 2023, 16(2): 91-95; ISBN: 1313-6917; Web of Science (CABI)

9.2 Publications in Bulgarian or foreign publications without indexation in SCOPUS and Web of Science:

- Д. Маринова, М. Дановска, Й. Тодорова, Т. Обрешкова, Е. Маринов. Невропсихиатрични нарушения при Болестта на Паркинсон – профил и оценка. Неврология и психиатрия, 2022, бр. 2, стр. 18-29, ISSN: 1311-6584

- • Д. Маринова, М. Дановска, Е. Маринов. Пандемията Covid-19 и болестта на Паркинсон. Неврология и психиатрия, 2022, бр. 1, стр. 27-39, ISSN: 1311-6584

9.3 Publications in scientific events with presentations/posters, with published abstracts in journals from forums in Bulgaria:

- Клиничен случай на пациент с хронична възпалителна демиелинизираща полиневропатия и миастения гравис, Й. Тодорова, В. Василева, М. Янакиева, Тр. Обрешкова, Д. Маринова, М. Дановска, XXI Национален конгрес по неврология, 2022
- Тромбоза на венозен синус с развитие на исхемичен мозъчен инсулт при бременна пациентка с доказан антифосфолипиден синдром - клиничен случай, Тодорова Й., Маринова Д., Обрешкова Тр., Василева В., Димитров Г., Дановска М., XXII Национален конгрес по Неврология, 18-21.05.2023г.
- Тромбоза на венозен синус с разпръснати исхемични зони при млад мъж с установено хетерозиготно носителство на фактор V HR2 и anti-Annexin V IGG, Тодорова Й, Стоев П., Маринова Д., Маринова-Трифонова Д., Василева В., Дановска М., XXII Национален конгрес по неврология, 18-21.05.2023г.
- Проучване на немоторни симптоми на болестта на Паркинсон при български пациенти Маринова Д.[1], Дановска М.[1], Иванов И.[2], Тодорова Й.[1], Обрешкова Т.[1], XXII Национален конгрес по неврология, 18-21.05.2023г.

9.4 Publications in scientific events with presentations/posters, with published abstracts in proceedings/journals from international forums:

- Age and gender-related differences of non-motor symptoms in patients with PD in Bulgaria, Desislava Marinova, Yoanna Todorova, Maya Danovska, AD/PD International conference on Alzheimer's and Parkinson's diseases and related neurological disorders, 05.-09.03.2024, Lisbon

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