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PREDICTION OF CLINICAL CONSEQUENCES OF PARKINSON'S DISEASE

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Parkinson's disease remains the most common neurodegenerative disease affecting 1–2 ‰ of the population. The aim of the study was to identify prognostically significant factors that determine the course of Parkinson's disease in the short term. The study was performed on the basis of the regional clinical hospital (Odesa) in 2017–2021. The data of the examination of 364 patients with verified Parkinson's disease , including 198 men (54.4 %) and 166 women (45.6 %), were analyzed. The average age of the patients was 63.2±0.6 years. There was found that the most significant predictors for predicting the course of Parkinson's disease are the severity of motor and cognitive disorders, the age of onset and the duration of the disease.

Key words: Parkinson's disease, diagnosis, prognosis, clinical outcomes, clinical monitoring

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ПРОГНОЗУВАННЯ КЛІНІЧНИХ НАСЛІДКІВ ХВОРОБИ ПАРКІНСОНА

Хвороба Паркінсона залишається найпоширенішим нейродегенеративним захворюванням, яке вражає 1–2 ‰ населення. Метою дослідження було виявлення прогностично значущих факторів, що визначають перебіг хвороби Паркінсона у найближчій перспективі. Дослідження проводилось на базі обласної клінічної лікарні (м. Одеса) у 2017–2021 рр. Проаналізовано дані обстеження 364 пацієнтів із верифікованою хворобою Паркінсона, з них 198 чоловіків (54,4 %) та 166 жінок (45,6 %). Середній вік хворих становив 63,2±0,6 року. Встановлено, що найбільш значущими предикторами для прогнозування перебігу хвороби Паркінсона є вираженість рухових та когнітивних розладів, вік початку та тривалість захворювання.

Ключові слова: хвороба Паркінсона, діагностика, прогнозування, клінічні наслідки, клінічний моніторинг

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Parkinson's disease (PD) remains the most common neurodegenerative disease affecting 1–2 ‰ of the population. The prevalence of PD increases with age, in the elderly it exceeds 1% of the total population over 60 years of age. Worldwide, disability and mortality due to PD are increasing faster than in the case of any other neurological disorder [4, 5].

In recent years, the interest of researchers in the search for clinical prediction tools in patients with PD has been increased. As a rule, the risk factors of decreased motility and the occurrence of persistent disability were evaluated, but there are also publications that mostly concern non–motor manifestations of PD [3, 9, 10]. Difficulties in quantitative assessment of disease progression, survival, disability, and quality of life are due to the lack of reliable tools and significant heterogeneity of the population of PD patients [9].

Existing prediction models are mostly based on linear regression equations [9, 11]. Their reproducibility is low, and the long–term prognosis is inaccurate [7].

Tang Y et al. created a model of survival in PD based on several available variables [11]. A multivariate model based on three features (age, disease duration, and disease stage) demonstrated the best predictive power in both the training and validation sets. The results suggest that the model can be used as a cost–effective tool for predicting the development of Parkinson's disease and assisting in clinical decision–making [11].

Currently, researchers are investigating new biomarkers for diagnosing and predicting mortality in patients with PD [8]. It is believed that priority should be given to easily accessible variables that are convenient to use in clinical practice. Often these relatively simple factors reflect more complex biomarkers. Thus, age is a contributing factor to the progressive decline in dopamine transporter binding in healthy individuals. The duration of the disease is also related to the progression of PD, but the age of the patients with PD affects the severity of the disease, regardless of the duration of the disease [3–5]. The Hoehn–Yahr scale is a widely used clinical standard for assessing the stage of PD [9]. Although this staging method is not tied to any pathophysiological correlation, it is very practical and allows independent experts to reproduce the assessment of the patient's overall functional level.

Many studies have studied monocausal prognostic factors for the development of PD disease [6, 8]. However, it is known that multivariate prognostic models show better accuracy for individual risk

factors [10]. Thus, univariate models are not suitable for multivariate diseases such as PD. Recently, studies have reported two models consisting of several traditional factors [7, 12]. Macleod A. et al. reported a model of PD mortality combining four variables (age, sex, severity of axial features, and Charlson comorbidity index) with moderate discriminatory power (AUC=0.75) [7]. A study by Velseboer D et al. found a three–variable predictor model with higher patient age, higher UPDRSME axial score, and lower fluency score conferring a higher likelihood of adverse outcome, with an AUC value of 0.765 [12]. However, these studies had several shortcomings. First, they used a small sample (fewer than 400 participants). Second, their models could only predict the probability of survival for a single point in time. Thirdly, in terms of life expectancy, patients with PD often do not differ from the general population, the question of greater interest for the clinician is not how high the risk of death is for a given patient, but how long he will remain compensated and not need outside help [3, 9].

The purpose of the study was to identify prognostically significant factors that determine the course of Parkinson's disease in the short term.

Material and methods. The study was performed on the basis of the regional clinical hospital (Odesa) in 2017–2021. The data of the examination of 364 patients with verified PD, including 198 men (54.4 %) and 166 women (45.6 %), were analyzed. The average age of the patients was 63.2±0.6 years. In 127 patients, a deepening of motor deficit was noted during the year of observation.

These records were later combined in the regional register of the main extrapyramidal diseases, the technical support of which was carried out using EDB Access (Microsoft Inc., USA).

When creating the register, they relied on the experience of domestic and foreign specialists. The unit of observation is a case of detected disease of the extrapyramidal system, the sources of primary information were forms 001o, 003o, 025o, 074o, 131o. Only disease cases of persons who permanently lived in Odesa region were included in the register

The created register contains the following content distractors (Fig. 1).

Code/service information	MRI	Agonists of dopamine
DOB	CT	receptors
Year of birth	Pisa Tower Syndrome	MAO inhibitors
Sex	Camptocormia	COMT inhibitors
Residence	Pace	Other medicines
Profession	Anosmia	Rehabilitation
Manufacturing hazards	Tremor	The area of the substantia
Does it currently work?	Salivation	nigra
Retired	Depression	Changes in the area of the
Invalidity	Chronic constipation	red nucleus
Hereditary history	On/off	Changes in the seam area
Genealogical history	Handwriting	Age-related changes with
Diagnosis	Propulsion	mild or moderate atrophy
The presence of PD	Thevenard's test	in the frontoparietal
Type of PD	Language	region
Stage by Hoehn-Yahr	Non-motor manifestations	Expansion of the
Hyperkinesis,	Intellectual disabilities	ventricular system
hallucinations	(1-4 points)	(internal hydrocephalus)
Score on the MMSE scale 0-	Disorders of self-care (5-	Mixed hydrocephalus
30	17 points)	Suffered strokes
Beck depression scale	Movement disorders (18-31	Date of last contact
score	points)	Date of death (in case of
PBT (pegboard test)	Age of disease onset	fatal outcome)
KSPP	Duration of illness	
UPDRS scale	Duration of treatment	
Used drugs	Coffee consumption	
Associated diseases	Smoking	
Duplex scan of vessels of	Levodopa	
the head and neck	Cholinolytics	
Ultrasound	Amantidines	

Fig. 1. Distractors for entering data into the regional register.

Regression models were determined by stepwise multiple linear regression analysis for each clinical task. Provided that the R2 of the exponential regression exceeded the R2 of the linear regression in terms of dimension, a preliminary logarithm of the data was used before performing the stepwise multiple linear regression analysis. The independent variable was excluded from the model if the adjusted R2 for each step of the regression analysis was insignificant ($p>0.05$) [1].

Linear discriminant regression analysis was used to distinguish different variants of the course of PD, assess severity and determine clinical prognosis. Multivariate analysis was performed using the method of principal components followed by orthogonal rotation using the Equamax normalized method. As an

event that was to be predicted by the factor model, a clinical deterioration of 1 point on the Hoehn–Yahr scale was taken, provided that the patient followed the treatment recommendations (adequate compliance).

All calculations were performed in the Statistica 13.0 software environment (TIBCO, USA) [2].

Results of the study and their discussion. A left–sided lesion was detected in 34.6 % of patients, a right–sided one in (34.9 %), a bilateral one in 111 (30.5 %). Akinetic–rigid form was determined in 92 (25.3 %) patients, trembling – in 27 (7.4 %) patients. Among the mixed forms, mixed rigid–tremor prevailed – in 157 (43.1 %) cases. Tremor–rigid was determined in 88 (24.2 %) cases.

Most of the patients with PD had stage 1–2.5 according to Hoehn–Yahr. Stage 1 according to Hoehn–Yahr was determined in 33 (9.1 %). These patients were characterized by a minimal duration of the disease and, as a rule, were detected by specialists at the level of outpatient polyclinic units in Odessa, Chornomorsk and Yuzhny.

Stage 1.5 was determined in 58 (15.9 %) patients, stage 2 – in 104 (28.6 %) patients. In all the above–mentioned cases, there were no manifestations of postural instability.

Stage 2.5 according to Hoehn–Yahr was determined in 36 (9.9 %) cases. These patients had postural instability, which, however, the patient was able to overcome. The level of danger of falling according to DYPAGS was minimal (12.2±1.1 points), but higher than for patients of stage 1–2 (7.8±0.6 points, $p<0.05$).

In 108 (29.6 %) stage 3 according to Hoehn–Yahr was determined, and in 25 (6.9 %) – stage 4. There were no cases of more severe PD in the registry.

When analyzing the results of the survey according to UPDRS I, it was established that in terms of the severity of changes in thinking, behavior and mood, the sample of patients with PD had sufficiently low indicators – on average, 4.9±0.7 points. According to UPDRSII, the average score was 17.7±0.9 points. According to UPDRS III, the average score was 32.1±1.2 points.

Most patients (349 or 95.9 %) at the time of inclusion in the registry were taking antiparkinsonian drugs, including 165 (45.3 %) – levodopa drugs. Motor fluctuations were present in 31 (8.5 %) patients.

Bradykinesia was observed in all PD patients. Signs of postural instability were identified in 168 (46.2 %) patients who corresponded to stages 2.5, 3 and 4 according to Hoehn–Yahr. Pronounced resting tremor was present in 234 (98.2 %) patients.

Patients with motor fluctuations (n=31) were evaluated according to UPDRS IV, the average score was 3.8±0.5 points. The average duration of off episodes was 3–4 hours per day. Levodopa–induced hyperkinesis occurred in 55 (15.1 %) patients.

The average age at which the first manifestations of PD were registered corresponded to 57.5±0.5 points, i.e. slightly higher than the average age of debut in other neurodegenerative diseases. On average, treatment was started – 8.2±0.2 years after the first symptoms appeared. Instead, the duration of treatment was 4.5±0.2 years.

In 105 (28.8 %) patients with PD, pronounced stooping was noted. Camptocormia occurred in 37 (10.2 %) patients, and Pisa Tower syndrome in 13 (3.6 %) patients.

Gait disorders characteristic for PD were identified in 236 (64.8 %) patients. 18 (4.9 %) patients were characterized by falls when walking sideways, backwards or forwards (DYPAGS >25 points), 23 (6.3 %) had a stuttering phenomenon with impaired gait initiation. In 9 (2.5 %) patients, when walking, there was shuddering, acceleration of gait with elements of propulsion. Phenomena of apraxia of walking, astasia–abasia were detected in 12 (3.3 %) patients. In 17 (4.7 %) patients, a lag was noted when walking one of the limbs.

Depressive symptoms were present in 63 (17.3 %) patients. Along with purely depressive symptoms, the patients had bradyphrenia and changes in attention switching, that is, there was a cognitive deficit. A total of 289 (79.4 %) patients had cognitive disorders among patients with PD. In other words, all patients with depression in PD had cognitive deficits, but not all patients with cognitive impairments had depression.

Constipation syndrome was noted in 193 (53.0 %) patients. Changes in handwriting were determined in 121 (33.2 %) patients.

In 59.3 % of patients there were manifestations of autonomic dysfunction in the form of blood pressure lability – 94 (25.8 %), heart palpitations –29 (8.0 %), hot flashes and a feeling of heat in the face – 14 cases (3.8 %). 167 (45.9 %) had sleep disturbances. 26 (7.1 %) patients complained of increased sweating, 17 (4.7 patients noted oily skin. A frequent phenomenon was emotional lability (72 cases or 19.8 %).

The first principal component (PC) was found to absorb, by definition, the maximum share of variance (29.0 %), while receiving maximum factor loadings from such variables as disease stage, degree of movement impairment (M) and self–care ability (SC), as well as from the severity of pain (P) (Table 1).

Table 1

Factor loadings after rotation. Clusters of loadings determining skewness factors for hierarchical analysis of patient parameters

Indices	Main components				
	1	2	3	4	5
Stage of disease	**0.835**	-0.145	0.047	0.233	0.144
Motor disorders	**0.805**	0.121	0.033	0.225	-0.240
Self–service ability	**0.802**	0.140	0.081	0.310	-0.243
Pain syndrome	**0.707**	-0.063	-0.260	0.095	0.295
Positive retropulsive (pull) test (Thevenard's test)	**0.694**	-0.113	-0.011	0.033	0.259
Duration of disease	**0.621**	0.294	0.119	-0.120	-0.433
Age of disease debut	-0.173	**-0.940**	-0.061	0.076	0.137
Age at the moment of examination	0.183	**-0.903**	0.032	0.005	-0.147
Substantia Nigra ipsilaterally	0.323	-0.130	**-0.852**	-0.004	0.043
Substantia Nigra contrlaterally	-0.321	0.097	**-0.804**	0.038	-0.188
Cognitive impairment	0.405	0.004	-0.007	**0.883**	0.009
Severity of depression	0.389	0.031	0.029	**0.870**	0.031
MMSE score	-0.340	0.168	0.070	**-0.486**	0.052
Gender (M=0; F=1)	0.069	0.045	0.113	-0.029	**0.771**
Explained dispersion	4.06	1.91	1.49	2.01	1.15
Part of total weights	0.290	0.137	0.106	0.143	0.082

Note: * – the factor is significant (F>0.70)

At the limit of significance are the factor loadings of the severity of postural instability, which was assessed using the Thevenard's test (TT) and the duration of the disease (DD). This first main component (MC) can be interpreted as a measure of the decline in quality of life at different stages of the disease.

The second MC explains 13.7 % of the variance, receiving negative factor loadings, primarily from the age of onset of the disease (DA) and, to a lesser extent, from the age (A) at the time of disease detection. Therefore, the second MC can be interpreted as a chronology of the disease or time. Phenotypically, this can be represented as earlier–onset and later–onset PD cases

The third MC absorbs 10.6 % of the variance caused by the size of the substantia nigra, primarily ipsilateral to the predominant lesion, to a lesser extent contralaterally. This MC can be interpreted as neuroanatomical.

The fourth GC explains 14.3 % of the variance and receives the maximum factor load from the presence of clinical signs of cognitive impairment (CI – cognitive impairment) and somewhat less from the severity of depression (SD – severity of depression), and also worth attention – from the quantitative assessment of the state of cognitive functions (on the MMSE scale). This complex of factors can be interpreted as cognitive and psychological.

The last MC absorbs another 8.2 % of the variance and is interpreted unambiguously as a gender aspect of the pathology.

The inclusion of stage and disease duration variables in the regression model practically does not affect the extent to which they determine self–care disorders (Table 2).

Table 2

Results of regression analysis for the dependent variable (self–care) R=0.856; R2=0.732; Adjusted R2=0.730; F (4.5) =335; p<10–4; SE: 3.2 points

Indices	R	Beta	SE Beta	B	SE of B	$t_{(489)}$	p
			Interc.	1,191	0.675	1.76	0.079
Motor disorders	0.81	0.631	0.029	0.357	0.017	21.6	10^{-6}
Congitive impairment	0.61	0.259	0.027	0.776	0.081	9.6	10^{-6}
Disease debut	0.50	0.091	0.028	0.803	0.245	3.27	0.001
Duration of disease	0.26	0.060	0.025	0.063	0.026	2.44	0.015

Thus, what is more important is not the period during which a person is ill, but rather the degree of compensation of motor and non–motor disorders. It is interesting that the factor analysis did not distinguish sensory or autonomic disorders as the main predictors of the course of the disease. Instead, indicators reflecting the function of intelligence and cognitive abilities in general turned out to be more significant. At the same time, the model chose both qualitative characteristics of cognitive deficits (the presence of complaints about impaired memory, attention, ability to plan activities) and quantitative ones (MMSE results).

Thus, temporal indices (age of onset of the disease and its duration until the moment of entry into the registry), as well as the severity of motor and cognitive disorders, had the greatest influence on the probable clinical deterioration.

Creation of registers of socially significant diseases in recent years is considered as one of the priority tasks of both national and international health agencies. There are several reasons for this. First, the registry facilitates the selection of patients for RCTs and cohort studies, conducting pharmacoeconomic analysis, and evaluating the effectiveness of diagnostics, treatment, and rehabilitation. Secondly, it is an important tool of clinical and epidemiological research [3, 5, 8, 9, 12, 13].

There are two options for epidemiological analysis. The first, descriptive, answers the question "What? Where? When?" and allows to identify some regularities among cases and populations. Based on these observations, hypotheses can be developed about the causes of these patterns and about factors that increase the risk of the disease. The second, analytical one, allows you to answer the question "Why? and How?" and therefore determine the relationship between exposure and health consequences, which involves the use of a cohort approach and the comparison of several observation groups, one of which is a control [1, 11]. If descriptive epidemiology describes the occurrence of a disease (or its determinants) in a population, analytical epidemiology aims to gain knowledge about the quality and degree of influence of determinants on the occurrence of a disease. Thus, we chose a complex research design, when after the primary analysis, which was based on the approaches of descriptive epidemiology, more in–depth analytical studies of the role of some factors in the development of certain manifestations of the disease or its complications were conducted [9, 10]. According to the calculations, such factors are primarily the age of onset of the disease and its duration, severity of motor and cognitive disorders.

Conclusions

1. The most significant predictors for the course of PD are the severity of motor and cognitive disorders, the age of onset and the duration of the disease

2. The most important factors for predicting the course of the disease turned out to be the factors described by us as "a measure of the decrease in the quality of life at various stages of the disease" (29.0 % of the variance, factor loading from such variables as the stage of the disease, the degree of movement impairment, the ability to self–care, the severity of pain) , "disease chronology" (13.7 % of variance, indices of the age of onset of the disease and age at the time of disease detection), "neuroanatomical" (10.6 % of variance: the size of the ipsilateral and contralateral substantia nigra), "cognitive and psychological" (8.2 % of the variance: the presence of cognitive disorders, severity of depression).

3. For various clinical forms of PD and other extrapyramidal diseases, it is advisable to form various preventive and treatment strategies, the common feature of which is the acceleration of the term determining the final diagnosis and the timely start of adequate therapy.

Prospects for further research are related to the development of multimodal prognostic scales suitable for use in clinical practice.

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