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PROGNOSIS FOR ENDOMETRIAL HYPERPLASIA PROGRESSION IN PREMENOPAUSAL AND MENOPAUSAL WOMEN BASED ON THE ANALYSIS OF CELLULAR IMMUNITY INDICATORS USING MULTIPARAMETRIC NEURAL NETWORK CLUSTERING

Many factors play a role in the progression of endometrial hyperplasia and the increased risk of malignant transformation. One of the important factors influencing pathological tissue remodeling is the immune response. However, changes in cellular immunity have not yet been systematized into specific patterns of immunological response in hyperplasia. Therefore, the implementation of easy-to-use and relatively inexpensive information technologies and risk factor analysis techniques is particularly important.

The objective of the study was to develop methods for predicting endometrial hyperplasia progression based on the analysis of morphological markers and indicators of cellular immunity using multiparametric neural network clustering.

Materials and Methods. The indicators of the cellular component of general immunity were determined in 43 pre- and menopausal women, of whom 31 patients were diagnosed with endometrial hyperplasia without atypia, and 12 women were otherwise healthy and formed the control group. For deeper analysis, we applied an approach based on multiparameter neural network clustering using NeuroXL Classifier for Microsoft Excel.

Results. In patients with endometrial hyperplasia, suppression of cellular immunity with a significant decrease in the percentage of all lymphocyte subpopulations was detected, whereas no significant changes in the immunoregulatory index were

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observed. It can indicate sufficient compensatory capabilities of the immune defense. The results of cluster analysis showed that in order to predict the progression of endometrial hyperplasia based on the analysis of the cellular immunity, it is important to consider the combination of reduced levels of CD3+ T-lymphocytes, CD4+ T-lymphocytes, and CD8+ T-lymphocytes, and increased levels of CD3+CD56+ NKT-like cells and CD56+ NK cells.

Conclusions. Neural network clustering was used to objectively classify patients into risk groups for progression of endometrial hyperplasia based on the results of clustering the studied indicators, which allows determining the significance of combined changes in certain parameters for disease progression prognosis.

Keywords: endometrial hyperplasia, cellular immunity, neural network clustering.

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ПРОГНОЗУВАННЯ ПРОГРЕСУВАННЯ ГІПЕРПЛАЗІЇ ЕНДОМЕТРІЯ У ЖІНОК ПРЕ- ТА МЕНОПАУЗАЛЬНОГО ВІКУ НА ОСНОВІ АНАЛІЗУ ПОКАЗНИКІВ КЛІТИННОГО ІМУНІТЕТУ ІЗ ЗАСТОСУВАННЯМ БАГАТОПАРАМЕТРИЧНОЇ НЕЙРОМЕРЕЖЕВОЇ КЛАСТЕРИЗАЦІЇ

Чимало факторів відіграють роль у прогресуванні гіперплазії ендометрія та збільшенні ризику злоякісного переродження. Одним із важливих чинників, що впливає на патологічне ремоделювання тканин, є імунна відповідь. Однак зміни клітинного імунітету ще не систематизовані у певних патернах імунологічної відповіді при гіперплазії. Тому особливо важливим є впровадження простих у використанні та відносно недорогих інформаційних технологій та методик аналізу факторів ризику.

Мета дослідження – розробити методики прогнозування прогресування гіперплазії ендометрія на основі аналізу морфологічних маркерів та показників клітинної ланки загального імунітету із застосуванням багатопараметричної нейромережевої кластеризації.

Матеріали і методи. Визначено показники клітинної ланки загального імунітету у 43 жінок пре- та менопаузального віку, з яких у 31 пацієнтки діагностовано гіперплазію ендометрія без атипії, а 12 жінок були практично здоровими та склали контрольну групу. Для глибшого аналізу було використано підхід із застосуванням багатопараметричної нейромережевої кластеризації за допомогою NeuroXL Classifier для Microsoft Excel.

Результати досліджень. У хворих на гіперплазію ендометрія виявлено пригнічення клітинного імунітету зі значним зниженням процентного вмісту всіх субпопуляцій лімфоцитів, але без істотних змін імунорегуляторного

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індексу, що може свідчити про достатні компенсаторні можливості імунного захисту. Результати кластерного аналізу показали, що для прогнозування прогресування гіперплазії ендометрія на основі аналізу клітинної ланки загального імунітету важливо враховувати поєднання знижених показників CD3+ Т-лімфоцитів, CD4+ Т-лімфоцитів і CD8+ Т-лімфоцитів та підвищених рівнів CD3+CD56+ NKT-подібних клітин і CD56+ NK-клітин.

Висновки. Нейромережеву кластеризацію застосовано з метою об'єктивного віднесення хворих до групи ризику щодо прогресування гіперплазії ендометрія за результатами кластеризації досліджуваних показників, що дозволяє визначити значимість саме комбінованих змін певних параметрів для прогнозу прогресування патології.

Ключові слова: гіперплазія ендометрія, клітинний імунітет, нейромережева кластеризація.

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ABBREVIATION

EH – endometrial hyperplasia

INTRODUCTION

Patients' quality of life depends on high-quality and effective diagnostics and treatment of diseases. First of all, it is possible to increase the effectiveness of treatment and diagnostics by the correct prediction of the disease course. This result can be achieved by using modern information technologies to analyze numerous parameters that change during the disease course, including morphological ones [1–3].

Information support for early diagnosis and prevention of diseases, timely provision of medical care to patients from various risk groups and individuals with socially significant diseases is crucial in improving the health of the population as a whole [4, 5].

The study of endometrial hyperplasia (EH) is primarily attributable to the high risk of malignant transformation, which is rapidly increasing in both prevalence and mortality [6, 7]. Among gynecological diseases, hyperplastic processes of the endometrium account for 15% to 50%. Atypical EH becomes malignant in 8% to 29% of cases, although EH without atypia can also develop into endometrial cancer (up to 3%). Hyperplastic processes are known to occur more often in pre- and menopausal women with an increased body mass index, but are also observed in half of infertility cases [8]. Given this, there is a large cohort of women who require verification of the patterns of changes in endometrial components (in particular, a stromal component) during hyperplastic processes, as well as atypia risk prediction.

One of the important factors that plays a role in tissue remodeling under pathological conditions is the immune response. It is known that there are quantitative and qualitative changes in immune blood cells in benign and malignant endometrial diseases [9, 10]. However, it is the local immune response that plays an essential role in tissue remodeling [11, 12]. T-cells ensure the restructuring of the stromal component of organs, thus influencing the functioning part. However, changes in cellular immunity have not been systematized into certain patterns during the development of EH.

Thus, the creation of integral immunological indicators of endometrial disease progression is a crucial component of improving diagnostic and therapeutic measures, and therefore the quality of life of patients, which will certainly be reflected in demographic indicators. At the same time, the implementation of easy-to-use and relatively inexpensive information technologies and methods is especially important for optimizing the prediction of the disease progression.

Objective: The study aimed to develop methods for predicting endometrial hyperplasia progression based on the analysis of morphological markers and indicators of

cellular immunity using multiparametric neural network clustering.

MATERIALS AND METHODS. 43 pre- and menopausal women were examined, of whom 31 patients had endometrial hyperplasia without atypia, and 12 women were otherwise healthy and formed the control group. The patients were undergoing treatment at Ternopil City Communal Hospital No. 2 and district communal hospitals of Ternopil region (Ukraine). Inclusion criteria for the study were pre- and menopausal age (>38 years), histologically confirmed endometrial hyperplasia without atypia [13, 14], and signed informed consent to participate in the study. The control group consisted of 12 women aged >38 years without EH and concomitant somatic diseases.

The first study group included 11 women without signs of disease progression (simple hyperplasia), and the second group included 20 patients with signs of disease progression (complex hyperplasia) [15, 16]. The average age of patients in group 1 was (48.8±1.5) years, in group 2 – (55.3±1.9) years. The control group consisted of women aged (50.3±1.6) years. With comparative analysis, indicators were determined by which the study groups significantly differed from each other. We also studied combined changes in parameters during disease progression.

The following indicators of cellular immunity were analyzed: average proportions (in percent) of T-lymphocytes, NK-cells, B-lymphocytes, and monocytes subpopulations. Phenotype indicators for CD3+ T-cells were identified as CD3+, CD19-; for T-helpers – as CD4+, CD8-; for cytotoxic T-lymphocytes (T-suppressors) – as CD4-, CD8+, for NKT-like cells – as CD3+, CD56+, for NK-cells – as CD3-, CD56+, for B-lymphocytes – as CD3-, CD19+, and for monocytes/macrophages – as CD14+ in each group. Measurement of cellular immunity indicators was carried out in the Synevo laboratory (Ternopil, Ukraine). The flow cytofluorometry method was carried out using a BD FACSCalibur cytofluorometer (BD Biosciences, USA). Histological studies of endometrial biopsies were performed at the Department of Pathology with Autopsy Course and Forensic Medicine of the I. Ya. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine using materials from the Ternopil Regional Pathological Bureau.

Statistical analysis of the study results was conducted using Excel 2016 and Statistica Version 12 software. The statistically significant difference between the general group vs. the control group was determined using the Mann-Whitney test, and between the groups of patients with vs. without signs of disease progression – using the Kruskal-Wallis H-test. For a more in-depth analysis and clustering of patients in the study groups in order to optimize the prediction of the disease course, multiparametric neural network clustering was applied using the NeuroXL Classifier add-in for Microsoft Excel [17–19].

Table 1 – Immune cell phenotypes in women with and without endometrial hyperplasia

Immune cell phenotype	**Control group (n=12)**	**General group (n=31)**
CD3+, % Me (Q1–Q3)	72.53 (69.16 – 75.96)	58.18* (54.52 – 61.21)
CD4+, % Me (Q1–Q3)	36.01 (33.64 – 38.45)	28.13* (26.82 – 29.78)
CD8+, % Me (Q1–Q3)	26.13 (22.65 – 27.10)	19.45* (18.07 – 22.56)
CD4+/CD8+ Me (Q1–Q3)	1.44 (1.29 – 1.69)	1.44 (1.35 – 1.54)
CD3+ CD56 +, % Me (Q1–Q3)	6.50 (5.14 – 7.66)	8.46** (7.53 – 13.46)
CD56+, % Me (Q1–Q3)	10.26 (8.25 – 12.96)	8.86 (7.50 – 11.33)
CD19+, % Me (Q1–Q3)	9.00 (7.25 – 12.45)	7.47*** (6.41 – 8.40)
CD14+, Me (Q1–Q3), %	8.45 (7.88 – 8.54)	5.40* (5.00 – 6.20)

*Note: * – p<0.001 vs. the control group; ** – p<0.01 vs. the control group; *** – p<0.05 vs. the control group*

RESULTS AND DISCUSSION. Histological examination of endometrial biopsies from all patients revealed signs of endometrial hyperplasia without atypia. Group 1 included patients with EH variant, in which an increased number of glandular and stromal elements without structural reorganization of the endometrium was histologically detected. Group 2 included patients with EH variant involving a changed shape of the glands and reduced stromal component, that is, the presence of structural changes, which indicated the progression of the disease.

The content of most phenotypes of lymphocytes and monocytes in the blood of examined women with endometrial hyperplastic processes (general group) significantly differed from that of the control group. Table 1 presents data on CD3+, CD4+, CD8+, CD3+CD56, CD56+, CD19+, and CD14+ cell counts.

Table 1 also shows the changes in the immunoregulatory index (CD4/CD8 ratio). In addition to the indicators of the general group, the relative content of immune cells was studied in the blood of patients with different EH variants (types) (Table 2).

Analysis of cellular immunity indicators in the general group of examined patients with hyperplasia revealed a statistically significant decrease in the average percentages of CD3+ ($p<0.001$), CD4+ ($p<0.001$), CD8+ ($p<0.001$), CD3+CD56+ ($p<0.01$), CD19+ ($p<0.05$), and CD14+ ($p<0.001$) cells compared to the control group, while the average percentage of CD56+ cells did not differ significantly ($p>0.05$) from the control group. At the same time, the immunoregulatory index (CD4+/CD8+) in patients of the general group did not differ significantly from that in the control group ($p>0.05$).

Table 2 – Immune cell phenotypes in women with different variants of endometrial hyperplasia

Immune cell phenotype	Study group		
	Control group (n=12)	**Group 1 (n=11)**	**Group 2 (n=20)**
CD3+, % Me (Q1–Q3)	72.53 (69.16 – 75.96)	60.23 (54.52 – 61.62)*	57.91 (54.41 – 59.42)*
CD4+, % Me (Q1–Q3)	36.01 (33.64 – 38.45)	28.38 (28.13 – 30.82)**	27.40 (26.52 – 29.36)*
CD8+, % Me (Q1–Q3)	26.13 (22.65 – 27.10)	20.82 (18.48 – 22.83)**	18.58 (17.51 – 20.12)**
CD4+:CD8+ Me (Q1–Q3)	1.44 (1.29 – 1.69)	1.37 (1.28 – 1.52)	1.46 (1.40 – 1.55)
CD3+ CD56 +, % Me (Q1–Q3)	6.50 (5.14 – 7.66)	8.24 (7.53 – 12.22)**	9.00 (7.50 – 13.85)**
CD56+, % Me (Q1–Q3)	10.26 (8.25 – 12.96)	8.59 (6.07 – 10.22)	9.21 (7.65 – 12.50)
CD19+, % Me (Q1–Q3)	9.00 (7.25 – 12.45)	7.78 (7.18 – 8.50)	6.96 (6.24 – 7.49)***
CD14+, % Me (Q1–Q3)	8.45 (7.88 – 8.54)	5.68 (5.04 – 6.76)*	5.22 (5.08 – 6.10)*

*Note: * – $p<0.001$ vs. the control group; ** – $p<0.01$ vs. the control group; *** – $p<0.05$ vs. the control group; **** – $p<0.05$ vs. the first group*

In patients of group 1, a statistically significant decrease in the average proportions of CD3+ ($p<0.001$), CD4+ ($p<0.05$), CD8+ ($p<0.001$), CD3+CD56+ ($p<0.01$), and CD14+ ($p<0.001$) cells was found compared to the control group, and the average proportions of CD56+ and CD19+ cells did not differ significantly ($p>0.05$) from the controls.

In patients of group 2, there was a statistically significant decrease in the average percentages of CD3+ ($p<0.001$), CD4+ ($p<0.01$), CD8+ ($p<0.001$), CD3+CD56+ ($p<0.05$), CD19+ ($p<0.05$), and CD14+ ($p<0.001$) cells compared to the control group, while the average percentage of CD56+ cells did not differ statistically significantly ($p>0.05$) from that of the control group.

A comparative analysis of cellular immunity indicators in patients of groups 1 and 2 revealed a significant ($p<0.05$) predominance of cytotoxic T-lymphocytes level in group 1. The average proportions of other lymphocyte subpopulations in patients in both groups did not differ significantly ($p>0.05$). The immunoregulatory index (CD4+/CD8+ ratio) in women

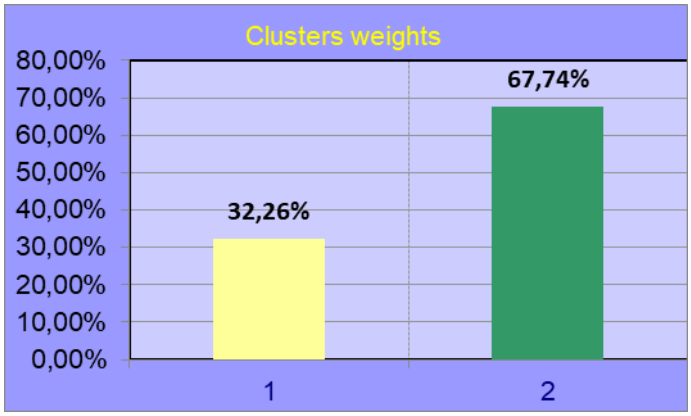
of groups 1 and 2 also did not significantly differ from that in the control group ($p>0.05$).

In order to establish the significance of combined changes in the cellular immunity parameters for predicting disease progression, multiparametric neural network clustering was performed. This study was conducted on the basis of the average proportions of lymphocyte subpopulations in patients of groups 1 and 2: 1 – CD3+ T-lymphocytes, 2 – CD4+ T-lymphocytes, 3 – CD8+ T-lymphocytes, 4 – CD3+CD56+ NKT-like cells, 5 – CD56+ NK cells, 6 – CD19+ B-lymphocytes, 7 – CD14+ cells. The disease progression indicator 8 ("P") was recorded opposite each patient in group 1 as "1" and in group 2 as "2".

To carry out neural network clustering, we chose the number of clusters to be equal to two. 32.26% of patients were classified into the first cluster, and 67.74% – into the second cluster (Fig. 1a).

The largest relative proportion of patients with disease progression was found in the 1st cluster. Using the cluster portrait (Fig. 1b), we determined that the first cluster also had the lowest values of the average proportions of CD3+ T-lymphocytes (1, -1.84%), CD4+ T-lymphocytes (2, -2.30%), CD8+ T-lymphocytes (3, -5.15%), CD19+ B-lymphocytes (6, -7.75%) and the highest values of CD3+CD56+ NKT-like cells (4, 1.78%) and CD56+ NK cells (5, 6.11%).

a)



b)

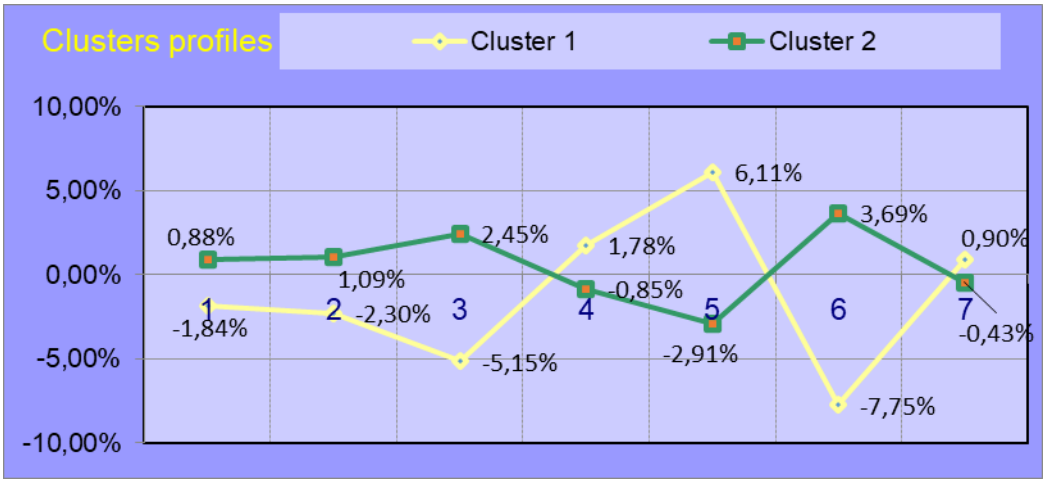


Figure 1 – Results of indicator clustering for patients with different variants of endometrial hyperplasia: a) cluster portrait – values of the studied parameters, including the average proportions of lymphocyte subpopulations and the disease progression indicators; b) cluster proportions – percentages of patients who fell into a certain cluster

In patients with EH, suppression of cellular immunity was detected with a significant decrease in the average proportions of all lymphocyte subpopulations compared to controls. At the same time, no significant changes in the immunoregulatory index were found, which could indicate sufficient compensatory capabilities of immune defense. In women with EH progression signs vs. the group of patients without EH progression, there was only a significantly lower proportion of cytotoxic T-lymphocytes, while other indicators of cellular immunity did not differ significantly. At the same time, the analysis of the

average proportions of indicators makes it impossible to establish the value of combined changes in certain parameters for predicting the disease course, in particular, disease progression.

At the same time, multiparametric neural network clustering taking into account the combined changes in cellular immunity parameters can objectively assign patients to the appropriate cluster – either with disease progression or with a stable condition. Thus, the results of cluster analysis showed that in order to predict the progression of endometrial hyperplasia based on the analysis of the cellular immunity, it is important to consider the combination of reduced levels of CD3+ T-lymphocytes, CD4+ T-lymphocytes, and CD8+ T-lymphocytes, and increased levels of CD3+CD56+ NKT-like cells and CD56+ NK cells.

In order to optimize the prediction of disease progression and improve early diagnosis and treatment, the following algorithm for step-by-step analysis of examination indicators in patients with EH is proposed. During the examination, the necessary indicators (average or relative values) are recorded, and a database is formed. To determine groups of indicators important for prediction, cluster analysis of data is performed, in particular using the NeuroXL Classifier program. In the future, the established combined changes in indicators, in particular cellular immunity, can be used in the work of a gynecologist or family doctor as markers for predicting disease progression in each individual clinical case.

The proposed approach, by the example of patients with EH, can be widely used to optimize the prediction of the course of other diseases when analyzing various clinical, anamnestic, and laboratory indicators. At the same time, a physician will need the help of an IT specialist only at the first stage. After conducting neural network clustering of the primary dataset of the studied parameters, the obtained results can be used in the future without expert opinion for each individual clinical case.

CONCLUSIONS

A method for predicting endometrial hyperplasia progression is proposed in this paper, which includes the analysis of relative values of cellular immunity indicators, in particular the average proportions of lymphocyte subpopulations, and the use of statistical analysis and neural network clustering algorithms.

Neural network clustering was used to objectively classify patients into risk groups for endometrial hyperplasia progression based on the results of clustering the studied indicators. It allowed the significance of combined changes in certain parameters to be determined for disease progression prognosis. The results of cluster analysis showed that in order to predict the progression of endometrial hyperplasia based on the analysis of the cellular immunity, it is important to consider the combination of reduced levels of CD3+ T-lymphocytes, CD4+ T-lymphocytes, and CD8+ T-lymphocytes, and increased levels of CD3+CD56+ NKT-like cells and CD56+ NK cells.

The developed method can be used by gynecologists, family doctors, or specialists in other specialties for early diagnosis of the progression of the most common diseases in a particular region. It is easy to use and does not require significant financial costs, which is important, in particular, in organizing diagnostic work at the primary level of medical care.

PROSPECTS FOR FUTURE RESEARCH

The proposed approach can be used in clinical studies to optimize the prediction of the progression of gynecological diseases and other disorders in order to correct examinations and develop new methods of treating patients.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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