Predictor factors of manifestation of concomitant kidney disease in rheumatoid arthritis patients

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Abstract. Based on the latest scientific evidence on the importance of infectious trigger factors in the manifestation of rheumatoid arthritis, chronic pyelonephritis among these triggers is one of the leaders. Great interest is also the probability of pyelonephritis manifestation while presence of RA. The aim of article was to investigate the possible interrelation between rheumatoid arthritis and manifestation of chronic pyelonephritis. A new method is based on cluster analysis and classification analysis, which identifies the main factors for the diagnosis and prognosis (β_2-microglobulin and MDA in urine, TGF-β in blood).

Keywords: *chronic pyelonephritis, rheumatoid arthritis, clustering, β_2-microglobulin.*

Introduction. Renal involvement in patients with rheumatoid arthritis (RA) is the most frequent and serious complication among other systemic manifestations and holds a special place in connection with a significant impact on prognosis and treatment approaches [1, 10, 14].

Today we know that one of the main factors likely occurrence and development of RA are external triggering factors among which the most important factor considered infectious, and its pathogenic effects to the body can be done in different ways [3, 10].

Latest scientific evidence show the importance of infectious trigger factors in the manifestation of RA, among these triggers chronic pyelonephritis is one of the leaders. Great interest is also the probability of pyelonephritis manifestation while presence of RA.

The aim of the study: to investigate the possible interrelation between rheumatoid arthritis and manifestation of chronic pyelonephritis.

Materials and methods. The authors examined 31 patients with RA II-III degree of activity with presence of chronic pyelonephritis (CP), 20 patients with RA without presence of CP and 20 healthy individuals. All patients who were included in the study, carried out a thorough examination using conventional clinical, laboratory, biochemical, and instrumental studies highly informative original modern research methods that are defined using uniform methods approved by the Ministry of Health of Ukraine. The presence of chronic kidney disease carried according to established classification adopted by the 2nd Congress of Nephrology Ukraine (September 24, 2005, Kharkov). We used to determine the glomerular filtration rate (GFR) using the formula of Cockroft DW and Gautl (Order of the Ministry of Health of Ukraine № 593 02.12.2004 "About the organization of medical care in the specialty "Nephrology").

In addition to conventional standard methods for the study of patients with renal and rheumatic disorders, in all patients were examined end products of lipid peroxidation (LPO) in blood and urine – malonic dyaldehid (MDA) [4, 12], β2-microglobulin (β2m) of blood and urine [13] and transforming growth factor β1 (TGF-β1) in blood using ELISA. The results of our previous studies showed that these markers have important role for early determination of progressive course of chronic kidney disease (CKD) in patients with RA [5, 6, 7, 8, 9, 11].

Clustering and classification methods Data Mining were used in order to identify factors predicting manifestations of chronic pyelonephritis in patients with RA [2]. Objects were clustered by multiple sets of the above factors into three clusters and the contents of data clusters were determined. If one cluster contains only healthy, the second - patients with RA, and the third - RA patients with chronic pyelonephritis, it should be a confirmation of the hypothesis. The following classification analysis helps us to establish the significance of factors and decide for diagnostic nosology. In addition, three different methods of clustering were used based on completely different mathematical theories to study possible links between RA and CP in patients with RA with the presence of CKD: the classic method of k-means, Kohonen maps (neural networks), fuzzy k-means (fuzzy logic).

Results and discussion. In values test of MDA in blood and urine it was found significant difference between groups of patients studied, indicating a significant increase in urinary MDA in patients with RA and CP ($p < 0.05$) and MDA blood mostly only in patients with RA ($p < 0, 05$) (Tab. 1).

Table 1. Characteristics of MDA in blood and urine of patients with RA with chronic pyelonephritis (M ± m, n)

Index	Group of healthy people (n = 20)	RA (n = 20)	RA with CP (n = 31)
blood MDA (mkmol/l)	17,03 ± 3,21	29,55 ± 2,02*	34,33 ± 2,12*
urinary MDA (mkmol/l)	6,56 ± 0,81	6,82 ± 1,21	11,87 ± 1,26*^
Notes:* – $p < 0,05$ probability relative to the group of healthy people ^ – $p < 0,05$ probability relative to group of patients with RA			

Results of the study β2m parameters in blood and urine, and TGF-β in blood showed a significant increase of TGF-β levels in patients in both studied groups, but in patients with joining of CP they were significantly increased ($p < 0.05$). β2m content in blood was significantly higher in patients with RA ($p < 0.05$), and urinary β2m content was significantly higher in group " CP + RA" ($p < 0.05$) (Tab.2).

Table 2. The content of TGF-β and β2-microglobulin in the blood and urine of patients with RA with the presence of chronic pyelonephritis (M ± m)

Index	Group of healthy people (n = 20)	RA (n = 20)	RA with CP (n = 31)
β_{2M} in blood (mkg/ml)	1,36 ± 0,01	1,98 ± 0,11*	2,14 ± 0,06*
β_{2M} in urine (mkg/ml)	0,20 ± 0,01	0,23 ± 0,02	0,89 ± 0,04*
TGF-β (mkg/ml)	54,49 ± 4,51	72,18 ± 1,99*	98,82 ± 2,31*^
Notes: * – $p < 0,05$ probability relative to the group of healthy people ^ – $p < 0,05$ probability relative to group of patients with RA			

Results of cluster analysis showed the following distribution of patients (tab. 3).

Table 3. Characteristics of results of qualification analysis according to the neural networks

Groups of patients				
	Classified			
IN FACT	Healthy	RA	RA + CP	Together
Healthy	20			20
RA		20		20
RA + CP			31	31
Together	20	20	31	71
Kohonen map				
	Classified			
IN FACT	Healthy	RA	RA + CP	Together
Healthy	20			20
RA		17		17
RA + CP			34	34
Together	20	17	34	71
k-means (fuzzy clustering)				
	Classified			
IN FACT	Healthy	RA	RA + CP	Together
Healthy	20			20
RA		15		15
RA + CP		1	35	36
Together	20	16	35	71

All studied group of healthy hit in a separate cluster (cluster 0). The findings are obtained by all three clustering methods. But in the diagnosis of RA and RA with the CP were observed differences. While building Kohonen maps patients with CP + RA got into a separate cluster (cluster "2"). Patients with only RA (20 patients), according Kohonen maps mainly hit the cluster "1" (18 patients). Some of them (3 persons) are classified as belonging to the cluster "2". Thus, these individuals must have two signs of disease, RA and CP, despite the fact that they are with diagnosed only RA. This means that these patients are at risk for CP. This analysis gives grounds to believe that RA may have signs of a factor which causes the manifestation of CP.

Results of clustering methods k-means and fuzzy clustering showed similar results about belonging to clusters. But dates of this method differ from previous methods. RA was diagnosed in 20 patients, but 5 are classified to the cluster of "2". In the second cluster there is also observed discrepancy – 1 patient is assigned to the cluster "1", that is to the patients with RA only. This indicates that the boundary between clusters RA and RA + CP s slightly blurred. To some extent this is a reason to consider that RA can be the basis of occurrence of CP. Particularly, in the analysis method of fuzzy clustering if for a new patient

$$\mu_2 = 0,02$$

received dates are: $\mu_0 = 0,95$, $\mu_1 = 0,08$ – it belongs to the cluster "0" at 95% and it means that person is healthy.

In case of $\mu_2 = 0,41$ – $\mu_0 = 0,01$, $\mu_1 = 0,55$, this correlates with belonging to RA (cluster "2"), even if the patient formally belongs to a cluster "1". It means that in the future in this patient can be diagnosed CP also.

The clustering method enables to confirm the connection between RA and CP. But it does not mean that this method determines the value of new rules of interrelation for patients and refer them to the different clusters. It doesn't give possibility to conduct a preliminary diagnostics without the introduction of information systems, which include these clustering methods. Based on this, the above rules may be built as a "decision trees" that can be obtained through analysis of neural networks classification. "Decision trees" are rules in a hierarchical structure that is consistent, where each object corresponds to a single node that makes the decision. For this, we used the method CART (Classification and Regression Tree). CART method is an algorithm for constructing of a binary decision tree (dichotomous classification model). n this

algorithm, each node of the decision tree has two descendants. The rule, which is formed in the node, in accordance to each step of building tree, divides a given a plurality of examples into two parts: the descendant RIGHT – the part in which rule is executed, and the descendant LEFT – the part in which the rule is not enforced. The function of assessment of quality division is used to select the optimal rule. So, neural networks realize this method.

Parameters that are "initial" – are the same factors, "output" – are the number of cluster. Thus, to establish the rules the classification analysis was conducted for the three initial fields: the actual diagnosis, cluster according to maps Kohonen, cluster by k-means (fuzzy clustering). Tabl.3 shows that in the first two cases neural network is fully capable to classify person's belonging to a particular cluster. In the case of fuzzy clustering we see only one mistake neural networks (attribution of patient with RA + HP to the first cluster). Therefore, considering specified accuracy of results, it is possible to represent "decision trees" and to determine the importance of factors for diagnosis. In the first case (the actual classification of diagnoses) level of urinary β_2m is a significant factor.

"Decision Tree" is presented in the table 4.

Table 4.

Diagnosis	β_2 – microglobulin in urine, mkg/ml
Healthy	β_2 – microglobulin in urine < 0,075
RA	β_2 – microglobulin in urine ≤ 0,075
RA + CP	0,075 ≤ β_2 – microglobulin in urine ≤ 0,171

As a result of the clustering method using Kohonen maps there were obtained such classification rules (tab. 5):

Table 5.

Diagnosis	urinary MDA (mkmol/l), β_2 – microglobulin in urine (mkg/ml), TGF-β, (pg/ml)
Healthy	β_2 – microglobulin in urine < 0,075
RA	8,113 ≤ urinary MDA < 11,692 β_2 – microglobulin in urine ≤ 0,075 ТФР-β < 99,224
RA + CP	urinary MDA > 11,692 0,075 ≤ β_2 – microglobulin in urine ≤ 0,171 TGF-β > 99,224

In such way significant indicators are MDA and β2m in urine, TGF-β in blood. It is shown that the rules for characteristics of healthy patient are coincide. But there is a difference in terms of TGF-β.

While using fuzzy clustering solution is slightly different from the previous ones, which is presented in tab. 6.

Table 6.

Diagnosis	urinary MDA (mkmol/l), β_2 – microglobulin in urine (mkg/ml)
Healthy	β_2 – microglobulin in urine < 0,075
RA	8,113 ≤ MDA in urine < 11,692 β_2 – microglobulin in urine ≤ 0,075
RA + CP	MDA in urine > 11,692 0,075 ≤ β_2 – microglobulin in urine ≤ 0,171

The main factor that characterizes the identity of the patient to the cluster of healthy is β2m in urine with the constant threshold value, but factor wich determines the membership of a type of disease is MDA in urine.

Conclusion. Usage this method makes probable of preliminary analysis of the mutual complication of RA and CP. A new method of diagnosing of factors and prognosis of RA and RA + CP based on cluster analysis and classification analysis, which identifies the main factors for the diagnosis and prognosis (β2-microglobulin and MDA in urine, TGF-β_1 in blood) can be used in clinical practice. This diagnostic method differs from conventional regression methods and is based on the using of cluster and classification methods for Data Mining and makes it possible to establish a relationship between a diagnosis of RA and manifestation of CP which is actually caused by RA. Using integration of these techniques into modern diagnostic systems will make possible to address the important issue of health care – improving of diagnosis and prognosis of kidney diseases.

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Факторы прогнозирования манифестации сопутствующей болезни почек у пациентов с ревматоидным артритом

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Аннотация. Исходя из последних научных данных о большом значении триггерных инфекционных факторов в манифестации ревматоидного артрита, хроническому пиелонефриту среди них отводится одно из ведущих мест. Большой интерес вызывает также вероятность манифестации пиелонефрита на фоне ревматоидного артрита. Цель исследования: исследовать возможную взаимосвязь между ревматоидным артритом и манифестацией хронического пиелонефрита. Новый метод основан на кластерном и классификационном анализе, который определяет основные факторы для диагностики и прогнозирования (β2-микроглобулин мочи, МДА мочи, ТФР-β_1 крови).

Ключевые слова: *хронический пиелонефрит, ревматоидный артрит, кластеризация, β_2-микроглобулин.*