Research Article

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Chemometric Expertise Of Clinical Monitoring Data Of Prolactinoma Patients

https://doi.org/10.1515/chem-2019-0050
received December 4, 2018; accepted December 31, 2018.

Abstract: The present investigation indicates hidden relationships between the several clinical parameters usually monitored on prolactinoma patients using non-hierarchical cluster analysis. The major goal of the chemometric data mining is to offer a possible mode of optimization of the monitoring procedure by selecting a reduced number of health status indicators. The intelligent data analysis reveals the formation of three patterns of prolactinoma patients each one of them described by a set of clinical parameters. Thus, better strategies for considering patients with this diagnosis could be developed and clinically applied.

Keywords: non-hierarchical clustering; prolactinoma; clinical indicators.

1 Introduction

Prolactinoma is a benign tumor (adenoma) of the pituitary gland which produces the hormone prolactin. Autopsy studies in the USA indicate that about 25% of the citizens have small pituitary tumors and that about 40% of them produce prolactin [1,2].

The cause of pituitary tumors remains unknown. It is established that stress can significantly raise the prolactin levels. This can make the stress a diagnostic parameter. In a very low number of patients, the level of cortisol (a hormone associated with stress) is determined.

The prolactin has a broad spectrum of biological actions which determine the metabolic control [3,4]. The symptoms caused by the hyperprolactinaemia are [3-7]: hypogonadotropic amenorrhea as a result of lowered follicle-stimulating hormone (FSH) levels; infertility; galactorrhea; loss of bone mass; hypogonadism; changes in the lipid metabolism.

The symptoms that are caused by the mass effect of the tumor upon the adjacent tissues are: bitemporal hemianopsia (due to pressure on optic chiasma); vertigo; nausea and vomiting. Except for the availability of prolactinoma, there are other reasons for moderate rise of the prolactin levels: the action of some medicines; existence of other pituitary tumors; pregnancy and lactation [8,9]. The prolactinoma medication has the aim to lower the prolactin secretion to the normal level, to correct visual impairments and to restore the normal function of the pituitary gland through lowering the size of the tumor. The dopamine suppresses the size of the tumor and lowers the prolactin levels in about 80% of the patients [10,11].

When the medication cannot be well tolerated or failed to reduce the prolactin levels, restoration of the normal pituitary function can be made through operative elimination of the tumor [12,13]. Depending on the size of the tumor and how much of it is removed, studies show that in 20 to 50% of patients it will reoccur usually, within five years [14,15].

There is a lack of specific studies trying to interpret in a multivariate way clinical data from prolactinoma patients. The aim of the present study is to reveal relationships between the clinical parameters monitored in prolactinoma patients and to establish if different patterns of similarity between the patients included in the group of observation exist or, on the contrary, the group of prolactinoma patients is homogeneous. The information obtained will be of use for possible optimization of the testing of the patients (e.g. reducing the number of observed parameters) or in finding discriminating factors for formation of different groups (patterns) of patients with similar medical status.

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2 Experimental

2.1 Clinical analysis

The data of forty six patients of the Clinic of Endocrinology, Medical University of Sofia are included. Thirty nine of them are females and seven are males.

All patients provided written, informed consent before the data delivery for statistical treatment study. The study was approved by the Scientific Research Board of Medical Faculty, University of Sofia and the clinical procedure for each patient was closely managed in accordance with the Declaration of Helsinki, local laws, and applicable regulatory requirements.

The next clinical parameters are used for the chemometric analysis:

1. **BMI**, body mass index, kg/m^2.
2. **ESR**, Erythrocyte sedimentation rate - the rate of the sedimentation of erythrocytes for a period of 1 hr. The reference values: up to 25 mm/h for women under 50 years and up to 30 mm/h for women over 50 years, up to 18 mm/h for men under 50 years and up to 22 mm/h for men over 50.
3. **HGB**, hemoglobin, reference values for women 120 - 160 g/L and for men 135 – 180 g/L.
4. **RBC**, red blood cells is a blood test, which presents the number of erythrocytes. Reference values for women (3.7 - 5.3) $\times 10^{12}$/L and for men (4.4 - 5.9) $\times 10^{12}$/L.
5. **PLT**, platelets, reference values (130 – 360) $\times 10^9$/L.
6. **Alb**, Albumin. Serum albumin is the main component of the blood plasma. Reference values for Alb: 35 - 53 g/L.
7. **Glu**, Glucose. The levels of the blood glucose are 2.8 - 6.1 mmol/L.
8. **Chol**, Cholesterol, reference values 3.4 - 5.2 mmol/L.
9. **LDL**, Low Density Lipoproteins, reference values 2.6 - 3.2 mmol/L.
10. **Trigl**, Triglycerides, reference values 0.6 - 1.7 mmol/L.
11. **ALAT**, alanine aminotransferase - catalyses two reactions of the alanine. This enzyme is a clinical index of the liver's status. Reference values 5 - 40 U/L.
12. **CK**, Creatine kinase or CPK, Creatine phosphokinase is the enzyme, which catalyses the conversion of creatine into phosphocreatine with adenosine triphosphate, ATP. Reference values for women 20 - 180 U/L and for men 30 – 200 U/L.
13. **Prol**, Prolactin is a hormone – glycoprotein secreted from the front lobe of the pituitary gland. It supports the production of the estrogens and progesterone. Prolactin stimulates the milk production. Reference values for women 59.3 - 619.0 mIU/L and for men 44.5 – 375.2 mIU/L.
14. **FSH,** Follicle-stimulating hormone is a glycoprotein hormone. It is synthesized and secreted from the front lobe of the pituitary (adenohypophysis). Reference values for women (follicular phase) 2.5 – 10.2 U/L and for men 1.4 – 18.1 U/L.
15. **Cortisol** is a steroid hormone secreted from the adrenal glands. It is regulated from the pituitary gland. Its level is the most raised at 8 h in the morning with reference values 118.2 - 618 nmol/L. The cortisol level is raised after physical and emotional stress and provokes decomposition of proteins and fats.

2.2 Chemometrics approach

In the present study, we used non-hierarchical cluster analysis (K-mean mode). It is an supervised clustering methods which allows preliminary selection of the number of clusters able to separate the variables (15 clinical indicators in our case) or the objects (46 cases or patients) into groups of similarity. This approach is well-known and widely used as a multivariate statistical technique [16] In order to cluster objects characterized by a set of variables (e.g. patients by clinical parameters), one has to determine initially the desired number of clusters due to preliminary hypotheses concerning the goal of clustering. Usually, preliminary information and experience is needed to construct a reliable hypotesis. A preliminary step of data scaling is necessary (e.g. autoscaling also called z – transform) where normalized dimensionless numbers replaces the real raw data values. Thus, even serious differences in absolute values are scaled to similar ranges.

3 Results and discussion

In Table 1 the basic statistics of the input data is presented.

3.1 Non-hierarchical clustering of the clinical indicators

Our hypothesis about the preliminary number of clusters able to describe the data structure of the input data set [46x15] supposed the formation of four clusters. It corresponds to the expert opinion that the prolactinoma status is closely related to factors like metabolic syndrome,

Table 1: Basics statistics.

Variable	Valid N	Mean	Minimum	Maximum	Std.Dev.
BMI kg/m^2	46	28.06	12.2	61.0	11.05
ESR mm/h	46	9.74	2.0	30.0	5.86
HGB g/L	46	135.59	99.2	161.0	13.40
RBC×10^{12}/L	46	4.51	3.37	6.0	0.58
PLT×10^9/L	46	242.33	69.0	441.0	71.48
albumin g/L	46	37.91	10.0	48.7	6.56
glucose mmol/L	46	4.77	3.5	7.3	0.62
cholesterol mmol/L	46	4.57	2.54	7.2	1.07
LDL mmol/L	46	2.94	1.27	5.7	1.01
triglycerides mmol/L	46	1.12	0.32	2.6	0.56
ALAT U/L	46	16.91	4.0	51.0	10.07
CK U/L	46	57.98	11.0	215.0	41.13
prolactin mIU/L	46	429.22	8.33	1334.0	369.12
FSH U/L	46	12.45	0.06	81.1	18.59
Cortizol nmol/L	46	354.76	7.44	728.0	184.50

blood quality, overall health status and disease related indicator levels.

K-means, non-hierarchical clustering offered the following grouping of the 15 clinical parameters measured:

Members of cluster 1: *BMI, Glu, Trig, ALAT, CK* (conditional name of the cluster – *metabolic syndrom factor* since it includes indicators directly related to the metabolic syndrom determinants);

Members of cluster 2: *ESR, PLT, RBC, HGB* (*blood quality* conditional *factor*, which includes all important blood parameters);

Members of cluster 3: *Chol, LDL, Alb* (*overall health status factor* as condcitional name);

Members of cluster 4: *FSH, PROLAC, Cort* (*hormonal factor* related to the course of the prolactinoma condition).

In Figure 1 the mean values (z-standardized values) of the separate clinical parameters included in each of the identified clusters for the whole group of patients is presented. It could be found that for all 46 cases (patients) different separation with respect to the clusters of indicators identified are present:

- Metabolic syndrome indicators (cluster 1) do not show any extreme values for the whole group of patients; related to this factor the gropu of 46 patients is homogeneous;

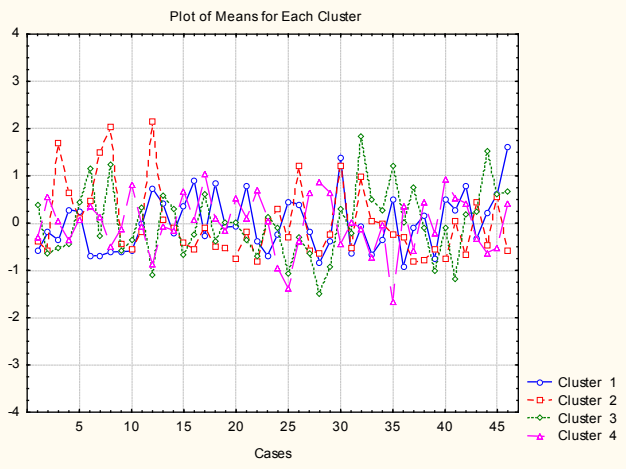

Figure 1: Plot of means for each identified cluster of clinical parameters for the whole group of patients.

- For a significant number of patients the blood quality indicators (cluster 2) are increased; therefore, a specific pattern of patients is formed;
- The same conclusion holds true for the impact of the clinical indicators included in cluster 3 (overall health status); again a pattern of patients with increased cholesterol, LDL and albumin level could be detected;
- Finally, the specificity of cluster 4 (related to prolactinoma symptoms) is not well expressed.

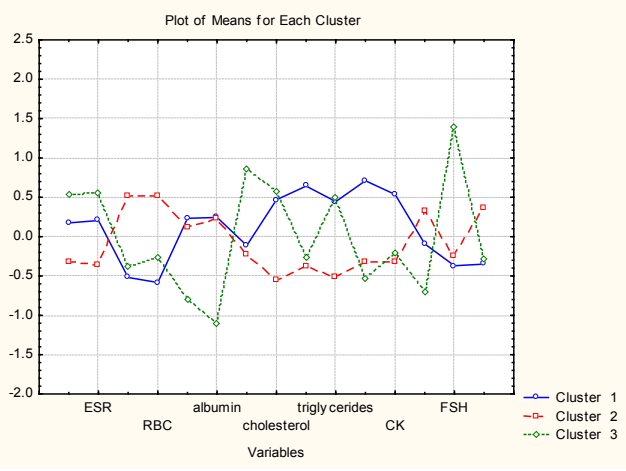

Figure 2: Plot of means of all clinical indicators for each cluster of patients.

This chemometric interpretation requires additional data interpretation by carrying out non-hierarchical clustering with respect to the objects of the study (patients).

3.2 Non-hierarchical clustering of the patients

We offered a hypothesis in this case requiring 3 clusters of patients with different health statuses: very good, intermediate, problematic.

Cluster 1 includes a total of 16 patiens with conditional numbers (*13, 14, 16, 18, 19, 21, 26, 32, 33, 35, 37, 42, 43, 44, 45, 46*)

Cluster 2 includes a total of 22 patients as follows (*1, 2, 6, 7, 9, 10, 11, 15, 17, 20, 22, 23, 27, 28, 29, 31, 34, 36, 38, 39, 40, 41*)

Cluster 3 contains the remaining 8 patients (*3, 4, 5, 8, 12, 24, 25, 30*)

It is interesting to note that the male patients are dominantly in cluster 1 (5 out of totally 7), and no male patient is included in cluster 3. It might mean that a relatively good separation with respect to sex is achieved. More important is, of course, to determine the specific discriminating clinical parameters for cluster 1, cluster 2 and cluster 3 of the patients.

In Figure 2 the mean values of all clinical indicators for each one of the identified clusters of patients are presented (z-standardized values).

The patients in cluster one are characterized as a pattern with "intermediate" health status (totally about 1/3 of all patients). The metabolic syndrome indicators are on average levels as compared to the other two groups of patients which have relatively low glucose and cholesterol levels registered and the hormone factors on an intermediate level. This is a "*background*" group of patients with satisfactory health status. Almost all male patients are included in cluster 1, which is an additional indication for relatively stable health status.

Cluster 2 content resemble the group of patients with "*best" health* status (this is a significant group of about 50% of all patients) which have good indications for metabolic factor indicators, best blood quality parameters and hormonal levels.

The smallest cluster 3 (only female patients, approximately15% of all patients) could be conditionally attributed to the *"worst" health* status since FSH hormonal levels are very high.

4 Conclusions

Specific relationships were revealed using the clinical parameters determined for prolactinoma patients. The formation of several clusters of similarity offers the opportunity for optimization of the procedure for clinical control by reducing the number of indicators necessary for rapid testing. Further, three various patterns of similarity between the patients included in the group of observation were determined: patients with good health status, patients with worse health status and patients with intermediate health status (almost all male patients included in this group of similarity). The extraction of the indicator clinical parameters for each pattern allows better decision making with respect to the health status of prolactinoma patients.

Acknowledgement. The authors would like to express their garitude to Bulgarian Scientific Fund DCOST Project 01/6 for the financial support. This work was supported by the project „Information and Communication Technologies for a Single Digital Market in Science, Education and Security" of the Scientific Research Center, NIS-3317.

Conflict of interest: Authors declare no conflict of interest.

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