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Methodological foundation of comprehensive support for dialysis patients based on artificial intelligence technologies

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***Abstract* — The existing software products represented by intelligent decision-support systems based on machine learning algorithms have minimal functionality and solve highly targeted problems in the field of hemodialysis. The aim of the study is to formulate the methodological foundations of the development of a medical information system that allows comprehensively addressing the quality of life problems of dialysis patients through the use of machine learning algorithms. A specific practical goal is to develop an intelligent decision support system for prescribing personalized dialysis and drug therapy for patients with chronic renal failure with an assessment of the long-term risks, as well as to assess the effectiveness of the treatment strategy in terms of the effectiveness of the hemodialysis procedure, the validity of prescriptions for restoring calcium and phosphorus metabolism and antianemic therapy based on the patient's profile. A patient's profile is understood as a combination of socio-demographic characteristics of the patient, functional examinations, laboratory and clinical studies of dynamics monitoring, the "history" of pharmacological prescriptions, and also (partially and not for all patients) genetic studies. The machine learning algorithms include: extreme gradient boosting over decision trees, matching, Cox regression (survival analysis). The significance of this study lies in the universality of the proposed methodology for creating an intelligent decision support system for prescribing personalized therapy to patients. The proposed technique can be used to create a similar medical system for other diseases. An important condition for the methodology translation for evaluating the effectiveness of the treatment of other diseases is the collection of data on patients under the constant supervision of a doctor for a long period of time. This applies to patients with diabetes mellitus, cancer patients, patients suffering from cardiovascular diseases.**

Keywords* — *hemodialysis, artificial intelligence, decision-support system, machine learning

I. INTRODUCTION

The downside of the general tendency to increase life expectancy in economically developed countries was an increase in the proportion of people who "survived" to the terminal stage of renal failure requiring dialysis therapy.

According to the latest published data from the All-Russian Register of Substitutive Renal Therapy of the Russian Dialysis Society, as of December 31, 2015 44,136 patients with end-stage chronic renal failure were receiving substitutive renal therapy (SRT) in Russia. In 2015 the growth rate of patients compared to the previous year was 11.6%, which was slightly higher than the average for 2010-2014 (10.8%) and, as in previous years, it was ahead of the trend of worldwide average values of this indicator, which had developed by the first decade of the 2000s. The prevalence indicator in Russia, that is, the number of patients provided with SRT per 1 million people, on average increased to 301.2 patients per million as of December 31, 2015. In most regions a clear tendency towards the development of SRT is observed during the operation of the register. [1].

According to the increase in the correctness of the health care, care for patients with end-stage renal failure should become more personalized. The backbone of personalized care is taking into account the needs and preferences of the patient, the progression of the disease, the response to treatment and the tolerance of dialysis therapy. One of the solutions for implementing personalized treatment strategies for dialysis patients is the introduction of information systems based on predictive modules utilizing machine learning algorithms for supporting the clinical decisions of doctors [2, 3].

The basis for constructing algorithms that correctly predict the outcome of therapy is qualitative information collected in sufficient volume. Today a MONDO registry exists [4], which includes data on more than 200,000 dialysis patients. However, the drawback of this registry is the inability to track the full history of appointments in retrospect, moreover, not only directly related to the hemodialysis procedure, but also with the achievement of targets for concomitant therapies, including hemoglobin, calcium-phosphorus metabolism, parathyroid hormone and other results of laboratory, clinical and functional examinations of the dialysis patient.

Presently there are studies on the use of artificial intelligence (AI) methods and machine learning algorithms in renal medicine, in particular, in dialysis. However, almost all of them are private and do not address the quality of life of dialysis patients in general. A fairly good review of this problem is described in [5]. There is a study [6] devoted to prediction of the total amount of water in the body in dialysis patients, based on neural networks, which is an assessment of the effectiveness of the dialysis procedure itself. Another study describes the use of AI technologies in predicting the consequences of anemia that occurs during hemodialysis [7]. A study using neural networks was also carried out [8], in which the task of predicting the concentration of parathyroid hormone in a patient's blood plasma as a result of calcium-phosphorus metabolism in dialysis patients is solved. Within a study [9.], based on retrospective data (6 months), a personalized dose of erythropoietins is selected as the main treatment against anemia. This solution is based on machine learning algorithms of the class of support vector methods. In [10] the risk of stroke in dialysis patients was determined on the basis of classification algorithms (naive Bayes classifier). As part of the study [11], the concept of full decision support for the appointment of antianemic therapy for dialysis patients based on neural networks was developed, which became the basis of the Anemia Control Model (ACM) program developed by Fresenius Medical Care. There is also an analytical system for managing the diagnostic and treatment process Maximus, developed by Diakea-Soft in partnership with the Medical and Educational Organization Nephrological Expert Council. The Maximus system allows for quick calculation and argumentation of the cost and payment of dialysis treatment, "maintains" an electronic patient history, allows collecting statistical data and has a predictive analytics module in the form of a primary diagnostic tool and predicting the possible development of dialysis therapy complications using neural network modeling [12].

From this perspective, the existing software products in the form of intelligent decision-support systems based on machine learning algorithms have minimal functionality and solve highly targeted problems. **The aim** of this study is to formulate the methodological foundations of the development of a medical information system that allows comprehensively addressing the quality of life problems of dialysis patients through the use of machine learning algorithms. A specific practical goal is the development of an intelligent decision-support system for prescribing personalized dialysis and drug therapy with the assessment of long-term risks for patients with chronic renal failure, as well as evaluation of the effectiveness of the treatment strategy in terms of the effectiveness of the hemodialysis procedure and the validity of prescribing to restore calcium-phosphorus metabolism (CFM) and antianemic therapy based on the patient profile. A patient's profile is understood as a combination of socio-demographic characteristics of the patient, functional examinations, laboratory and clinical studies of dynamics monitoring, the "history" of pharmacological prescriptions, and also (partially and not for all patients) genetic studies.

II. Research Methodology

The requirement for high accuracy and correctness of the proposed solutions is a unique feature of the development of decision support systems in medicine, since the price of error is human life and health. That is, the development of such systems should take into account many combinations of variables and cause-and-effect relationships related both to the patient's profile and to the characteristics of the prescribed treatment itself. It's quite difficult to take all this into account for a person and to describe it in the form of condition action rules, however, machine learning algorithms can easily cope with this task as part of AI technologies. The only condition for obtaining high predictive accuracy based on the developed machine learning algorithms is a large amount of collected correct data.

Thus, in order to achieve this goal methodology and tools for collecting and marking data, as well as the quality and quantity of patient data, are extremely important. That is why the intelligent module of a doctor's decision-support system is inseparable from the medical information system of the dialysis center. As a medical system for data collection, a specialized Lexema-Medic dialysis medical ERP system developed by LLC Ekosoft was used. The system is developed in Web architecture, the holding structure of the system allows all remote units of dialysis centers to work in a single information environment, manages workflows, determines the schedule of dialysis procedures, keeps records of patient registration cards, dialysis procedures, prescriptions for drug therapy, and laboratory test results. The system is integrated with the information system of the Invitro laboratory to obtain data on the results of high-quality laboratory tests. All these methods of constructing a dialysis center information system made it possible to obtain a large amount of data (data from almost 2,000 patient registration cards) of high quality (reliable and without omissions) for training models.

The basis for the development of machine learning algorithms that are accurate in terms of prediction is a correctly formed labeled selection of sufficient volume. Knowledge bases are used in this study based on an expert survey of nephrologists to mark up data from the point of view of the effectiveness and ineffectiveness of therapy, as well as the insufficiency and redundancy of the therapy used, if it is classified as ineffective. The consistency of expert opinions is checked based on the calculation of the Kendall concordance coefficient and the Friedman criterion, where expert opinions are considered consistent with the deviation of the null hypothesis of lack of consistency at $p < 0.05$. MySql query forms are used to simplify the marking of data on efficiency/inefficiency or redundancy/insufficiency. Sampling technologies are used for transition to balanced samples: in particular, oversampling, SMOTE and ASMO. The principal component method is used to reduce the attribute space, which allows taking into account more symptoms without losing the accuracy of the algorithms for predicting the effectiveness/ineffectiveness of therapies. Machine learning algorithms, such as extreme gradient boosting over decision trees and logistic regression, as well as a random forest algorithm, are used as methods for assessing the efficiency or inefficiency of therapies directly related to the hemodialysis procedure, antianemic therapy, and therapy for restoring the patient's calcium and phosphorus metabolism. The advantage of boosting technology, in contrast to the technology of neural networks, is the virtual indisposition for retrain, and, as a result, better adaptability to new data, which is fundamentally important when using the proposed solution for patients with different population characteristics. The procedures of cross validation with the selection of the optimal number of folds and "blind" validation, involving training ML algorithms in 70% of the sample and testing the results in 30%, are used to achieve the accuracy of the constructed models. The following metrics are used for the classification quality: model peculiarity (correct guessing of ineffective therapy and redundant); sensitivity (correct guessing of effective therapy and insufficient); F-measure, AUC (area under the ROC-curve as a general indicator of the quality of classification). Since the classification problem is solved for medical problems, the acceptable quality is: achieving specificity and sensitivity of the algorithms over 98%, F over 0.95, AUC over 0.95. The principal novelty of the proposed approach in terms of evaluating the effectiveness of therapies, from the point of view of achieving the target parameters of a blood test, in contrast to the ones discussed above, is the possibility of identifying the reasons for the ineffectiveness of the prescribed treatment (from the point of view of both the insufficiency and the redundancy of therapies), based on a larger number patterns of the patient's profile, including the qualitative ones.

The matching algorithm is used to select the most suitable therapies and characteristics of the dialysis procedure with this profile for the patient. The quality criterion in matching is considered to be the compliance of the therapy with the patient's profile by at least 80%. Correspondence should be sought on the basis of precedents (more than 9,000 records in the form of a correspondence between the patient's profile, his treatment (prescribing drug products with dosages and injection method) and the effectiveness of therapy in terms of changing clinical and diagnostic blood parameters. The authors of the study adapted the matching algorithm by taking into account all the parameters for finding the best fit with the scales that were put down during an expert survey of nephrologists, and as a result of repeated testing of the proposed methods. This leads to a mixed type algorithm that takes into account the results of matching and restrictions on the tolerability of specific drug products by each patient, thereby achieving the optimal treatment strategy for the patient, taking into account his individual characteristics. The advantage of this solution is the possibility of presenting three patient treatment strategies to the doctor, indicating the probability of its compliance with the effectiveness (over 80%) with an estimate of the cost of each treatment for a month of use.

The machine learning tools apparatus, Survival analysis, is used to assess the consequences of long-term dialysis therapy, such as stroke and other hemorrhagic lesions of organs. A period of up to 2 years is considered as the period of onset of the adverse effects of long-term dialysis therapy, and a pool of adverse events is determined for the patient resulting from the long-term use of renal replacement therapy driven by guidance of nephrologists. Information criteria of Akaike and Schwartz are used for selection of survival models, where a model with the lowest values of these criteria is selected. A log-rank test (Cochran-Mantel-Haenszel test), Gehan-Wilcoxon test and Peto-Peto test are used for the selection of predictors of the risk of death for dialysis patients and the onset of other adverse events in the form of hemorrhagic organ damage. Survival models are evaluated based on the maximum likelihood method with the selection of a function in the Efron form. Such an approach allows to determine not only the likelihood of adverse effects (as in the classic existing classification problems), but also to determine the timing of the onset of such consequences, based on the patient's profile and retrospective of clinical diagnostic and functional examinations, as well as the characteristics of the dialysis procedure referred for him.

It's worth noting that the approaches, methods and ways of integration with any devices that underlie the development of the proposed system make it easy to adapt it to other business processes for the provision of comprehensive dialysis treatment, whether it is home dialysis or a mobile artificial kidney.

III. Results of the Research

The following steps were performed to achieve the goal based on the proposed research methodology.

At the first stage of the research, rules for marking up the efficiency and inefficiency, as well as insufficiency or redundancy, of anti-anemia therapy and restoration of calcium-phosphorus metabolism were formed based on an expert survey of nephrologists. Thus, a knowledge base of expert evaluations of doctors was created. Doctors were interviewed without the possibility of a meeting to achieve indicators of high accuracy of estimates for marking up data; this approach made it possible to virtually eliminate controversial issues regarding the classification of therapy in various classes. The consistency of expert opinions was checked on the basis of the Kendall concordance coefficient ($W = 0.654$), the statistical significance of which was confirmed by the Friedman criterion ($p = 0.0002$), which made it possible to draw a conclusion on the consistency of opinions. MySQL from was written to verify the resulting markup. As a result, the correctness of the marked data was checked independently by 2 expert doctors who were not involved into the development of rules regarding the effectiveness of therapy; errors in markup were less than 0.3%. The main criteria for the effectiveness of the therapy was considered to be the achievement of the target parameters of blood tests of patients.

As a result, a complete pool of parameters for training the model according to the marked data was for anti-anemic therapy was created: gender and age of the patient, body mass index, hepatitis B, hepatitis C, HIV infection, month of treatment: "Epocrin" dosage, "Eralfon" dosage, "Selamerex" dosage, "Mircera" dosage, "Mimpara" dosage, "Ferrum 3 complex" dosage, "Calcium carbonate" dosage, "Velphoro" dosage, "Aranesp" dosage, "Alpha D3-Teva" dosage, "Parsabiv" dosage, "Erythropoietin" dosage, "Zemplar" dosage, hemoglobin, ferritin, potassium, sodium, white blood cells, hematocrit, thrombocytes, red blood cells, glucose, albumin, creatinine, phosphorus, urea, iron, parathyroid hormone, calcium, cholsetirin, protein,% transferrin saturation with iron, vitamin D, phosphatase, KT/V, plasma bicarbonate, hemoglobulin last value, hemoglobulin value before last, fertility, duration of prescribed erythropoietins, the value dynamics of hemoglobulin within a month, the value dynamics of hemoglobin within three months, duration of dialysis treatment. As a result, the complete pool of parameters for the treatment of phosphorus-calcium metabolism disorders was: IICP, patient name, gender, age, body mass index, hepatitis B, hepatitis C, HIV infection, month of treatment, “Epocrin” dosage, “Eralfon” dosage, "Selamerex" dosage, "Mircera" dosage, "Mimpara" dosage, "Ferrum 3 complex" dosage, "Calcium carbonate" dosage, "Velphoro" dosage, "Aranesp" dosage, "Alpha D3-Teva" dosage, "Parsabiv" dosage, "Erythropoietin" dosage, "Zemplar" dosage, hemoglobin, ferritin, potassium, sodium, white blood cells, hematocrit, thrombocytes, red blood cells, glucose, albumin, creatinine, phosphorus, urea, iron, parathyroid hormone, calcium, cholsetirin, protein,% transferrin saturation with iron, vitamin D, phosphatase, KT/V, plasma bicarbonate, PTH last value, PTH value before last, calcium last value, calcium value before last, phosphorus last value, phosphorus value before last, the value of PTH dynamics within a month, the value of PTH dynamics within three months, the value of phosphorus dynamics within a month, the value of phosphorus dynamics within three months, the value dynamics of calcium last month, the value dynamics of calcium within three months. The dosage of the drug products was taken as the total for the entire month of treatment, the analysis values were taken following the course of treatment within a month. Also, for the records of the treatment of anemia artificial parameters were introduced: criteria - the type of prescribed erythropoietin preparations (short or long-acting); fertility of a woman (yes or no). A woman is considered fertile if her age is from 15 to 45 years; interval - the value of hemoglobin within month of treatment; hemoglobin value one month before treatment; the value of hemoglobin dynamics within one month (the value after treatment minus the value before the treatment order); the value of hemoglobin dynamics within three months (the value after the treatment order minus the value one month before the treatment order). The following parameters were artificially introduced for the records of the treatment of phosphorus-calcium metabolism disorders: PTH value per month of the treatment order; phosphorus value per month of the treatment order; calcium value in the month of the treatment order; PTH value one month before the treatment order; phosphorus value one month before the treatment order; calcium value one month before the treatment order; the value of the dynamics of PTH for one month (the value after the treatment order minus the value before the treatment order); the value of the dynamics of phosphorus wirhin one month (the value after treatment minus the value before the treatment order); the value of the dynamics of calcium within one month (the value after the treatment order minus the value before the treatment order); the value of the dynamics of PTH within three months (the value after the treatment order minus the value one month before the treatment order); the value of the dynamics of phosphorus within three months (the value after the treatment order minus the value one month before the treatment order); the value of the dynamics of calcium within three months (the value after the treatment order minus the value one month before the treatment order). The attributes were transformed by means of SVD decomposition and using the principal component method to reduce the attribute space.

At the second stage the calibration of the obtained labeled data was carried out. For the training of classification models (classifying therapy as effective/ineffective) for anti-anemic therapy (AT), 9,158 records were received, and therapy for the restoration of phosphorus-calcium metabolism (PhCM) records. The samples were balanced in relation to the presentation of each class: 45% of records for PhCM were among ineffective therapy, and 61% for AT. In order to determine among the inefficient therapies the insufficient and excessive there was the following class representation, respectively: for AT - 22%, for PhCM - 8%. The sampling method was used to switch to balanced samples in this case: in particular, oversampling, SMOTE and ASMO. Thus, all training samples were balanced, which significantly increased the reliability of predictive analytics models when separating classes of insufficient or inefficient) therapy from excessive.

At the third stage direct training of models predicting the effectiveness of antianemic therapy and therapy for the recovery of PhCM was provided. “Blind” validation, involving training ML algorithms in 70% of the sample and testing the results in 30%, are used to achieve the accuracy of the constructed models. As machine learning algorithms we used: extreme gradient boosting over decision trees and logistic regression, random forest algorithms. As metrics of the classification quality, we used indicators obtained from the conjugacy matrix of correctly and incorrectly guessed cases: model peculiarity (correct guessing of ineffective therapy and redundant); sensitivity (correct guessing of effective therapy and insufficient); F-measure, AUC (area under the ROC-curve as a general indicator of the quality of classification).

As a result, the following quality metrics were obtained on a test sample to evaluate the effectiveness/ineffectiveness of therapy: for anti-anemic (gradient boosting algorithm): sensitivity 98.9%, specificity 98.2%, F = 0.989, AUC = 0.99; for therapy for the recovery of FCF (gradient boosting algorithm): sensitivity 98.4%, specificity 98.3%, F = 0.98, AUC = 0.985. As a result, the following quality metrics were obtained on the test sample to assess the inefficiency/redundancy of the therapy: for anti-anemic (random forest algorithm with oversampling): sensitivity 98.4%, specificity 97.7%, F = 0.99, AUC = 0, 98; for therapy for the recovery of FCF (extreme boosting algorithm with oversampling): sensitivity 99.5%, specificity 100%, F = 0.997, AUC = 0.995. Based on the metrics obtained during blind validation, we can conclude that the classification of therapies is very predictive in accuracy. Algorithms are tested on data from 24 dialysis centers in the following regions: Udmurtia, the Khanty-Mansi Autonomous District.

At the fourth stage, the matching algorithm was used to select the most suitable therapies and characteristics of the dialysis procedure with this profile for the patient. Matching quality was considered to be a criterion of quality for matching the therapy to the patient’s profile by at least 80%. Conformity was sought on the basis of precedents (more than 9,000 records in the form of a correspondence between the patient’s profile, his treatment (prescribing drug products with dosages and injection method) and the effectiveness of therapy in terms of changing clinical diagnostic parameters of blood. The authors of the project team adapted the matching algorithm by taking into account all the parameters for finding the greatest match with the weights that were put down during an expert survey of nephrologists, and as a result of repeated testing of the proposed method. The result was a mixed-type algorithm that takes into account the results of matching and restrictions on the tolerability of specific drug products by each patient, thus achieving the optimal treatment strategy for the patient, taking into account his individual characteristics and compliance with accepted treatment standards. The advantage of this solution was that the doctor was presented three patient treatment strategies, indicating the likelihood of its compliance with the effectiveness (over 80%) with an estimate of the cost of each treatment for a month of treatment. Currently these algorithms are undergoing testing on the data of 24 dialysis centers in the following regions: Udmurtia, the Khanty-Mansi Autonomous District.

At the fifth stage, all classification and matching algorithms implemented in python were integrated into an ERP system serving hemodialysis centers, the software implementation of which was implemented using node.js and the Javascript programming language.

IV. Discussion of results

One of the quality criteria for the development of any medical information system that allows a comprehensive consideration of the quality of life of patients is not only the accuracy of diagnosis, the effective treatment order and risk assessment of complications, but also the economic effect of the introduction of such a software product.

So, on-line monitoring of the effectiveness of therapy and the construction of a recommendation system containing effective recommendations in this research, as well as with the subsequent use of its results, will make the most optimal use of the funds allocated for this therapy.

For example, an evaluation of the effectiveness of treating patients on dialysis within 2018 with machine learning methods, already carried out within the framework of the project, revealed a significant percentage of the ineffective treatment performed at the high cost of the therapy itself for dialysis patients, namely, 48% of ineffective antianemic therapy and 46% of ineffective therapy restoration of phosphorus-calcium metabolism. Upon reaching the project target - 95% of the accuracy of the performance evaluation, the increase will be about 47% on average.

In Russia the costs of the hemodialysis procedure, based on the lifelong need for 156 sessions per year (3 times a week for 4 hours), amount to more than 750,000 roubles per patient annually, and taking into account the drug product supply, from 1 million to 1.5 million roubles. Thus, the cost of drug therapy is from 250 to 750 per year per patient.

In the Russian Federation, according to 2015 alone, almost 35 thousand patients were using hemodialysis. According to expert estimates, the annual growth of patients with renal replacement therapy applied to is 10%. Consequently, with an increase in efficiency by 47%, the project will allow funds allocated to ineffective therapy to be redirected to effective treatment regimens, which will be from 822,500 to 2,467,500 thousand roubles only for domestic dialysis centers.

This example shows that the development of an intelligent decision support system for prescribing personalized dialysis and drug therapy to patients with chronic renal failure, as well as evaluating the effectiveness of the treatment strategy in terms of the hemodialysis procedure effectiveness, the validity of the prescriptions for the restoration of phosphorus-calcium metabolism (FCM), and antianemic therapy based on the patient profile is an urgent task for dialysis centers.

Algorithms are tested on data from 24 dialysis centers in the following regions: Udmurtia, the Khanty-Mansi Autonomous District.

V. Conclusion

The significance of this study lies in the universality of the proposed methodology for creating an intelligent decision support system for prescribing personalized therapy to patients. The proposed technique can be used to create a similar medical system for other diseases. An important condition for the translation of the methodology for evaluating the effectiveness of the treatment of other diseases is the collection of data on patients under the constant supervision of a doctor for a long period of time. Such patients include patients with diabetes mellitus, cancer patients, patients suffering from cardiovascular diseases.

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