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PROSPECTS FOR THE USE OF ARTIFICIAL NEURAL NETWORKS FOR PROBLEM SOLVING IN CLINICAL TRANSPLANTATION

R.M. Kurabekova[1], A.A. Belchenkov[1], O.P. Shevchenko[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

Management of solid organ recipients requires a significant amount of research and observation throughout the recipient's life. This is associated with accumulation of large amounts of information that requires structuring and subsequent analysis. Information technologies such as machine learning, neural networks and other artificial intelligence tools make it possible to analyze the so-called 'big data'. Machine learning technologies are based on the concept of a machine that mimics human intelligence and and makes it possible to identify patterns that are inaccessible to traditional methods. There are still few examples of the use of artificial intelligence programs in transplantology. However, their number has increased markedly in recent years. A review of modern literature on the use of artificial intelligence systems in transplantology is presented.

Keywords: artificial intelligence in transplantation, machine learning, expert system, artificial neural network.

INTRODUCTION

Solid organ transplantation is one of the most high-tech and knowledge-intensive fields of modern medicine. Therapy for solid organ recipients requires a significant amount of research and observation, both before transplantation and after surgery, throughout the recipient's life. Routine follow-up of recipients include a wide range of imaging, clinical and laboratory methods, which necessitates analysis of large volumes of data [1].

The accumulated data on patients and various procedures are typically stored in specialized databases [2, 3], scientific registries [4] and in medical histories. As these data and procedures increase in volume, there is a natural need for tools that can be used to analyze the so-called "big data". In recent years, information technologies, such as machine learning, neural networks and other artificial intelligence tools, have been increasingly used in biomedical research, mainly in fields involving large volumes of complex data, such as genomics and bioinformatics [5]. The number of examples of AI applications in transplantology is small, but they have noticeably increased in number in recent years [6–10].

Although the terms '*artificial intelligence*', '*machine learning*' or '*artificial neural networks*' are widely used in the literature, the essence of these methods, their capabilities and weaknesses are not fully understood [11, 12].

The aim of this study is to review the current literature on application of artificial intelligence (AI) systems for solving problems in transplantology.

A review of foreign and Russian research publications in the publicly available databases of Pubmed, Russian Science Citation Index, CyberLeninck and Google Scholar for the past 5 years, using keywords ("artificial intelligence", "machine learning", "artificial neural networks", "transpl*") and their combinations, enabled us to find over 6000 papers, of which about 30 were related to transplantology.

TERMINOLOGY

Artificial intelligence (AI) is the general name for a number of computer technologies, such as expert systems, computer vision, robotics, machine learning, etc., that are based on the concept of a machine simulating human intelligence. The first expert systems began to be used as early as the 1970s, for example, to interpret electrocardiograms. More significant advances were made at the beginning of the 21st century in the field of image recognition [13].

The main features of AI are considered to be the ability to analyze data, applying different algorithms to achieve given goals, analyze and tune the performance of algorithms, and then apply them to new data, repeating and updating the previous process and data samples.

AI technology, like any other technology, uses a large number of terms and definitions that require specialized knowledge to understand. Below are simplified definitions of the most commonly used terms in this field.

Machine learning (ML) is a class of artificial intelligence methods and a class of computer programs that

Corresponding author: Olga Shevchenko. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation.
Phone: (499) 190-38-77. E-mail: transplant2009@mail.ru

can, by performing certain tasks, improve and increase problem-solving performance over time and as new data are introduced in the program.

Expert system is a subset of machine learning. It is built on the basis of decision-making rules. A computer model is trained (to solve specific problems, e.g., prediction) using statistical theories/methods or by identifying certain patterns/regularities in the data.

Deep learning (DL) is a set of machine learning methods based on learning representations, rather than specialized algorithms designed to solve specific problems. In practice, deep learning, also known as deep structured or hierarchical learning, uses a large number of hidden layers of nonlinear processing to extract features from data and transform data to different levels of abstraction (representations). Artificial neural networks are created using deep machine learning methods.

Artificial neural network (ANN) is a mathematical model, as well as computer software, built on the principle of organization and functioning of biological neural networks – networks of epy nerve cells of a living organism. ANN is a system of interconnected and interacting simple processors (artificial neurons). Each processor of such a network deals only with signals it periodically receives and signals it periodically sends to other processors. Neurons are organized into layers. The number of layers for each network is individual and depends on the applied problem being solved. Technically, neural networks are not programmed, but trained. Learning is a process of finding coefficients of connections between neurons.

Decision tree is a tree-like flowchart structure with internal nodes, branches and leaves. The internal nodes contain questions (e.g., does the patient have fever >39 °C), branches represent the answer (e.g., yes or no), and the leaves represent the final definition of data classes (e.g., sick or healthy).

Random forest is a machine learning algorithm consisting of a set of decision trees.

K-nearest neighbor is a machine learning algorithm for solving classification and regression problems based on similarity (e.g., proximity or distance) between available data and new data.

Naive Bayes is a machine learning algorithm that uses probabilistic classifiers based on Bayes' theorem that assumes no relationship between predictor variables.

K-means clustering – an algorithm that identifies similar characteristics of data in a set and divides them into subgroups.

Various types of learning models are used in machine learning, which are not described in this paper [14–16].

EVALUATION OF AI MODELS

When analyzing the results obtained with ANN-based models, it is important to understand how adequate they are, what the performance of the model is, and whether it has been adequately validated. Usually used for this purpose are performance characteristics that are similar to those used for evaluating traditional tests, calculated using ROC analysis: AUROC (area under the receiver operating characteristic), C-statistic (sensitivity and specificity), and metrics such as accuracy, positive predictive value, negative predictive value, and F1 scores [17].

AI-based models, like traditional statistical models, must be validated in a different patient population, at a different center, or under different conditions. Model performance may change with new data, e.g., a different CT image resolution obtained with a different scanner, a different electronic medical record system, etc. Therefore, it is important to pay attention to whether the model has been externally validated.

AI IN TRANSPLANTOLOGY

Risk prediction plays an important role in clinical trials in transplantology. Most risk assessment models are based on regression analysis, which allows us to determine the nature of the relationship between predictors and outcomes [18]. However, such models have many disadvantages: they only allow estimating a limited number of predictors that are assumed not to change throughout the life of the participants. Besides, these methods do not allow for analysis of nonlinear relationships, often require data conversion into binary form, and do not allow for analysis of large datasets. Deep machine learning methods provide ways of overcoming these shortcomings [19, 20].

Much of the work on the use of AI in transplantology is devoted to solving survival and rejection problems, mainly in kidney or liver recipients [21–29]. Other important tasks to be solved by machine learning methods are selection of compatible donor/recipient pairs [7, 30], prediction of graft dysfunction [31–33], and selection of optimal immunosuppression regime [8, 34, 35].

Tapak et al. used machine learning algorithms to predict primary graft dysfunction as an important criterion for liver transplantation [36]. Machine learning was used to select 15 main donor, recipient and graft characteristics affecting the development of graft dysfunction within 30 days after transplantation. Based on the 15 donor and recipient parameters determined before transplantation, algorithms were developed to predict graft dysfunction with a mean AUROC of 0.835 – using ANN.

Several machine learning algorithms, including a neural network, were tested in Miller et al. using data from the United Network of Organ Sharing (UNOS) database from 1987 to 2014 [37]. The authors evaluated the 1-year survival of heart transplant recipients and compared the results with a standard statistical model based on logistic regression. They used 80% of the data as a training sample and 20% for validation. C statistic evaluation of the models showed that the neural network had characteristics (AUROC = 0.66) similar to those of logistic regression (AUROC = 0.65). The authors concluded that the machine learning algorithms, derived from the original dataset they used, were not superior to traditional methods. However, they suggested that AI could outperform traditional statistical methods if augmented with new data from e-medical records.

In Reeve et al. [38], AI was used to assess the prognosis of renal transplant rejection. Clinically confirmed biopsy results were used to verify the diagnosis of T cell-mediated and antibody-mediated rejection. AI-based algorithms showed a higher level of accuracy compared to the accuracy obtained by physicians (92% for T cell-mediated rejection and 94% for antibody-mediated rejection).

Bertsimas et al. developed an optimized mortality prediction model (OPOM) for predicting the 3-month waitlist mortality in liver recipients [39]. The work used a large data set including 1,618,966 observations and various machine learning methods, including neural network and logistic regression. In liver transplantation, when the OPOM model was used for donor organ allocation, there were 41,796 fewer recipient deaths per year compared with the traditional MELD system: the AUROC for OPOM was higher than that for MELD: 0.859 and 0.841, respectively. The authors showed that the OPOM model is also suitable for patients with hepatocellular carcinoma, but the model requires external validation: there are plans for the model to be tested on a new group of patients.

I. Scheffner et al. derived a survival prediction model for kidney recipients [40]. A retrospective cohort of kidney recipients who underwent biopsy after transplantation according to the protocol was divided into data sets for training and validation. The model demonstrated good performance using data before kidney transplantation, as well as data 3 and 12 months after the surgery. Apart from previously established age, cardiovascular disease, diabetes and graft function, the effectiveness of graft rejection therapy and urinary tract infections were found to be important predictors of patient survival.

ADVANTAGES AND DISADVANTAGES OF AI

Machine learning methods are versatile tools that can be widely applied to a variety of problems in transplantology. However, like any other analytical method, machine learning has its strengths and weaknesses. The strengths of machine learning include the ability to detect patterns and trends that cannot be detected using the classical statistical methods, and the ability to process multidimensional and diverse data. An important feature of machine learning technology is the ability to improve the accuracy and efficiency of predictions as experience and data volume increase.

A weakness of machine learning is the difficulty in interpreting results, which in some cases may not make biological sense and have no practical application. In addition, large amounts of data are needed to ensure the accuracy of the results when training an algorithm or model. As with conventional diagnostic or predictive models, the quality of inferences drawn from AI algorithms depends on the characteristics of the dataset used to train the model. As with conventional methods, it is important to consider the inclusion and exclusion criteria of the study. For example, a model to predict liver transplant survival based on donor/recipient pair compatibility may be inaccurate for recipients with hepatocellular carcinoma if the input dataset did not include enough of such patients.

CONCLUSION

Machine learning algorithms can be valuable tools for supporting a decision-making process on donor organ allocation, level of risk of post-transplant complications, or selection of an immunosuppressive therapy regimen, which is particularly relevant in settings, where suboptimal donor organ use can worsen waitlist or post-transplant mortality. The use of artificial intelligence can help to gain new insights from "old" data and make a significant contribution to improving transplant outcomes and survival rates in solid organ recipients.

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