

# Systematic Review of Supervised Machine Learning Models in Prediction of Medical Conditions

Short title: Supervised Machine Learning Models in Prediction of Medical Conditions

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## ABSTRACT

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Machine learning (ML) models for analyzing medical data are critical for both accelerating development of novel diagnostic and treatment strategies and improving the accuracy of medical care delivery. Our objective was to comprehensively review supervised ML models for diagnosis or treatment prediction. Publications indexed in PubMed were reviewed to identify articles utilizing supervised predictive ML models in medicine. Articles published between 01/01/2020–01/01/2022 were included in this review. Initially, PubMed was searched using MeSH major terms, and if more extensive search results were needed, a broader search was applied (titles/abstracts). PubMed indexed 21,268 published articles (MeSH Major topic) describing ML methods implemented in medicine. Of those, 11,726 articles were published within the last 2 years. Most of the published ML models in medicine in the last two years were different types of deep learning models (about 75%). Fifty articles were included in this review. Almost all categories of disease were subjects of ML predictions. Positive and negative factors in each of the scenarios need to be evaluated before the most optimal ML model is selected. Domain knowledge and collaborations between physicians and ML experts can improve the selection and prediction performance of ML models in medicine and facilitate implementation in clinical practice. Predictive ML models could provide recommendations to recruit suitable patients for clinical trials. Prediction ML models may contribute to development of more effective diagnostic and therapeutic choices, founded on evidence-based medicine. A broad range of methodological approaches have been taken toward this goal, and those approaches are presented here with their various advantages and disadvantages.

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## AUTHOR SUMMARY

62 Over the last decade, there has been rapid development of Machine learning (ML) methods to analyze  
63 Big Data in medicine. ML is aimed to make the computer learn from past experiences and make  
64 predictions by recognizing patterns in medical data. We performed a comprehensive systematic literature  
65 review of recent publications (last two years), indexed in PubMed/MEDLINE that have described either  
66 traditional or deep supervised prediction ML models in medicine. We identified 21,268 articles  
67 describing ML implementation in medicine. 11,726 articles were published in the last 2 years. We  
68 presented the number of publications describing each of the most often ML methods to show current  
69 trends in development of these models. Most of the recently published ML models in medicine were  
70 deep learning models. We found that the understanding of disease is likely to lead to more accurate  
71 prediction. An important dilemma is the selection of optimal ML models for a specific task, considering  
72 amount and type of available data. Domain knowledge and collaborations between physicians and ML  
73 experts can improve the prediction performance of ML models, which could help clinicians to select the  
74 most effective diagnostic and therapeutic choices available and decrease medical errors.

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## 78 INTRODUCTION

79 Over the last decade, there has been significant growth of the amount of medical data generated by the  
80 adoption and integration of electronic health records (EHR).[1] This growth in EHR data coincided with  
81 rapid development of ML techniques and computing power to analyze Big Data in medicine, which  
82 could contribute to improved medical solutions and better, more efficient healthcare.[2-5] ML is a branch  
83 of Artificial intelligence (AI), aimed to make the computer learn from past experiences and make  
84 predictions by recognizing patterns in medical data.[5-7] ML can be classified into three categories:

85 unsupervised, supervised, and reinforcement learning (RL). This paper focuses on supervised ML  
86 techniques, where a function that maps an input to an output is inferred from labeled training data.  
87 The objective of the research was to perform a comprehensive systematic literature review of recent  
88 publications that have used either traditional or deep supervised prediction ML models in medicine. We  
89 examined whether the method is appropriate for the selected medical prediction task, whether the model  
90 is generalizable, and whether it could be used by clinicians to improve the quality of medical care.  
91 Supervised prediction ML models are utilized in traditional and deep learning approaches.[5-7] The most  
92 frequently used traditional ML models in medicine are: decision trees (DT),[8] random forest (RF),[9]  
93 and other ensemble methods,[10-14] single and multi-layer perceptron (MLP),[15.16] Bayesian learning  
94 (BL),[17] support vector machines (SVM),[18] k-nearest neighbors (k-NN),[19] linear regression  
95 (LR),[20] and logistic regression (LogR).[21] Deep learning models are inspired by biological neural  
96 networks, where each layer of the network learns higher order features of the previous layer. Different  
97 types of neural networks have been designed, such as: deep neural networks (DNN) including deep belief  
98 networks,[22] convolutional neural networks (CNN),[22] recurrent neural networks (RNN - long short-  
99 term memory (LSTM) and gated rectified unit (GRU)),[23] etc.  
100 Many ML models have been developed for prediction of diagnosis, or recommendation of the most  
101 optimal therapeutic approach. Since this is a rapidly evolving scientific field, we reviewed articles  
102 published within the last two years.

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## 104 **MATERIALS AND METHODS**

105 We conducted a systematic review of articles describing supervised prediction ML models (traditional  
106 and deep learning) published within the last two years (01/01/2020 –01/01/2022). The following  
107 traditional supervised ML models were included in the review: DT, RF and other ensemble methods, the

108 perceptron, BL models, SVM, k-NN, LR, and LogR. Deep learning models included in the review were:  
109 DNN, CNN, and RNN.

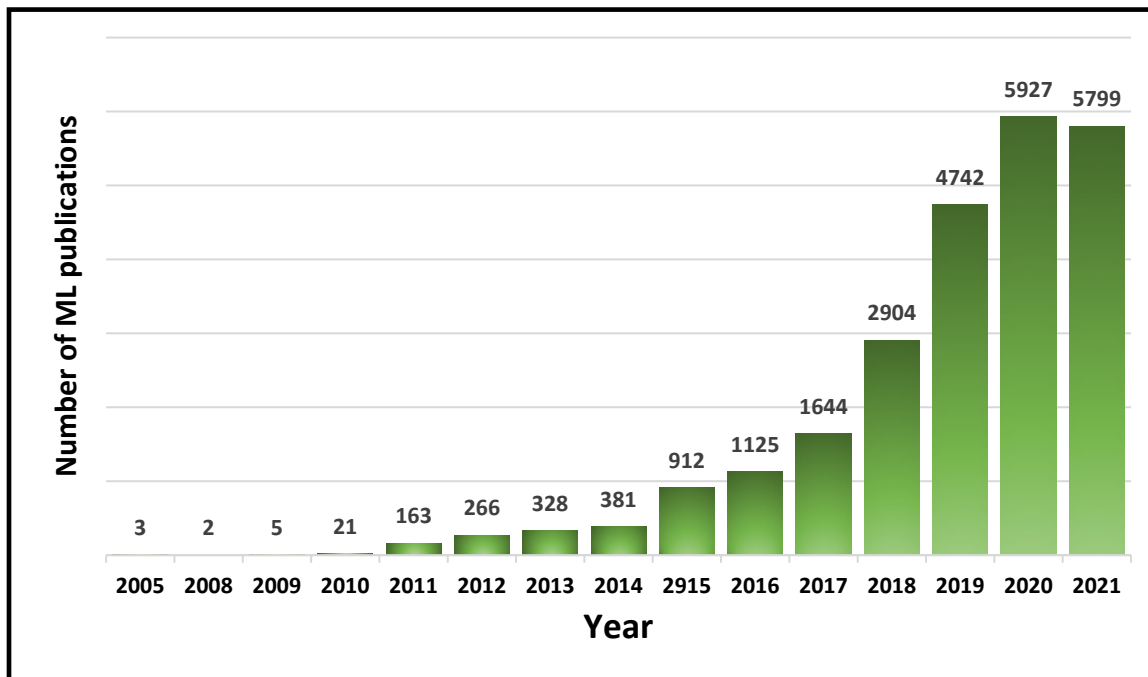
110 We searched PubMed/MEDLINE, as the most relevant source of medical topics, to identify articles  
111 describing applications of supervised traditional and deep predictive ML models in medicine. Initially,  
112 we searched PubMed using MeSH (Medical Subject Headings) major terms. If we did not find enough  
113 literature for the specific ML model, we applied a broader search using terms that appear in titles of  
114 publications, or in case of bagging and boosting ensemble models and RNN we used combinations of  
115 MeSH and title/abstract searches. This searching approach extracted articles where the reviewed ML  
116 model was a major part of the article. The search strategy used keywords indicating “ML model” AND  
117 “prediction/detection/classification” AND “medical conditions (therapies, outcomes)”. In the example  
118 of deep learning methods, we divided searches into 3 groups: classic DNN, CNN and RNN. To extract  
119 general DNN models we used the following search query: ("deep learning"[Mesh] not "CNN" not  
120 "RNN" not "LSTM" not "GRU"). For CNN models the query was: (CNN[Title]) OR (convolutional  
121 neural networks[Title]). And for RNN model the query was: (RNN[Title/abstract] OR recurrent neural  
122 networks[Title] OR LSTM[Title] OR GRU[Title] OR long short term memory[Title] OR gated rectified  
123 unit[Title]).

124 We included articles that presented original research published in English. The search results were sorted  
125 according to types of described ML models. For each of the reviewed ML models we selected a  
126 representative sample. Priority was given to the newest published research in cases of multiple papers  
127 describing similar predictive ML approaches. At least four authors agreed that the article was sufficiently  
128 significant to be included in this review. We performed a systematic review of the literature to analyze  
129 how useful and meaningful the described predictive ML models are in terms of realistic applicability in  
130 medical practice.

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132 **RESULTS**

133 We identified 21,268 articles (MeSH Major topic) describing ML implementation in medicine (Figure  
 134 1). 11,726 articles were published in the last 2 years.



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137 Figure 1. Number of publications describing ML applications in Medicine indexed in PubMed.

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141 Fifty articles were included in the review. In Table 1, we present the method of search for each of the  
 142 ML models and the number of publications retrieved using that particular search method. Most of the  
 143 published ML models in medicine in the last two years were different types of deep learning models.

ML method	Type of ML	Type of PubMed Search	% of articles total	% in the last 2 years
Linear regression	Traditional	MeSH Major topic	13%	1%
SVM	Traditional	MeSH Major topic	13%	4%
DT	Traditional	MeSH Major topic	9%	1%
Logistic regression	Traditional	MeSH Major topic	9%	1%
Bayesian	Traditional	MeSH Major topic	5%	4%
RF	Traditional	MeSH Major topic	8%	8%
Ensemble - boosting	Traditional	Title search	1%	1%
k-NN	Traditional	Title search	3%	2%
Perceptron	Traditional	Title search	1%	1%
Ensemble - bagging	Traditional	Title search	1%	1%

DNN	Deep	MeSH Major topic	27%	35%
CNN	Deep	Title search	13%	22%
RNN	Deep	Title search	10%	14%

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145 Table 1. Supervised ML methods applied in prediction of medical conditions. Percentages of articles of  
146 the total number of publications by ML method are presented.

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### **Traditional models**

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**Decision trees** are classification methods that adopt a top-down strategy where each node represents a  
150 classification question and the branches partition the data into different classes.[8] DT models were  
151 developed for prediction of diabetes mellitus type 2 (DM2), and essential hypertension (EH),[24] by  
152 creating visually guided classification trees to facilitate the feature selection (four different datasets, sizes  
153 547 – 12,447). The prediction accuracy of DM2 and EH in different scenarios varied between 58% and  
154 87%. DTs predicted coronary artery disease with the accuracy about 91% on a dataset of 303  
155 patients.[25] A DT algorithm was proposed to identify pre-treatment clinical predictors of survival in  
156 rectal cancer (100 examples).[26] Predicted accuracy of survival rates were 71-76%. Presented DT  
157 models have questionable generalization potential, since most of them were developed on small samples  
158 frequently from one hospital.

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**Random Forest** is a ML method that applies many decision trees to predict the outcome.[9] RF models  
160 have been constructed to predict hepatotoxicity on a dataset of 346 samples, with the accuracy up to  
161 71%.[27] This may provide a basis for improved safety evaluation in drug discovery and the risk  
162 assessment of environmental pollutants. A retrospective review of 559 patients undergoing abdominal  
163 hernia was the basis for RF modeling to predict surgical approach and determine the importance of  
164 different socioeconomic variables in selecting the type of surgery (area under the receiver operating  
165 characteristic (AUROC)  $\approx 0.82$ ).[28] Data were obtained from a single institution, which limits the  
166 generalizability of findings. Psychotic and depressive symptom clusters in dementia were predicted  
167 using RF on the EHR records of 4,003 patients with dementia (AUROC 0.80).[29] An RF model boosted

168 by the AdaBoost algorithm was utilized to predict the severity of COVID-19 cases and the possible  
169 outcome, by using a patient's geographical, travel, health, and demographic data (3397 patients, accuracy  
170 94%). The model revealed a positive correlation between patients' genders and deaths, finding that men  
171 are more likely to die.[30] All presented RF models need further improvements including potential  
172 combination with deep learning ML models to find a relevant application in practice.

173 **Ensemble Methods** (boosting, bagging) combine a few weak learning models and turn them into a great  
174 learning algorithm.[10-14] The most famous boosting algorithm is AdaBoost. ML models were built to  
175 predict the probability of different pairs of drugs and nanoparticles creating drug-decorated nanoparticle  
176 (DDNPs) complexes with anti-glioblastoma activity. Forty-one features have been selected for 855,129  
177 drug-nanoparticle complexes. The best model was obtained with the bagging ensemble classifier, based  
178 on 20 decision trees with the AUROC of 0.96 and accuracy of 87%. This model could be applied for the  
179 screening of nanoparticle-drug complexes in glioblastoma.[31] The bagging ensemble method improves  
180 reproducibility of both cortical and subcortical functional parcellation of the human brain neuroimaging  
181 (more than 300 samples).[32] AdaBoost was used to differentiate colorectal neoplasia from normal tissue  
182 (AUROC up to 0.95 on 64 samples from 16 patients).[33] Both models use imaging data as inputs and  
183 need additional research work, including comparison to deep learning models, before their potential  
184 application in clinical practice.

185 **Perceptron and Multilayer Perceptron.** The perceptron is based on a threshold function that learns  
186 weights for features and processes one example at a time. It could be used as a single-layer perceptron  
187 or as a multilayer perceptron.[15,16] Modeling of the spread of the COVID-19 infection using a MLP  
188 was designed on a dataset (20,706 examples) operated by the Johns Hopkins University Center for  
189 Systems Science and Engineering (JHU CSSE).[34] This is one of many papers about COVID-19  
190 intended to predict the spread of the infection, but the model lacks generalization ability. MLP was  
191 applied in a diagnosis of breast cancer subtypes, using MRI images (704 images) with AUROC of



192 0.86.[35] The study used imaging data to distinguish between benign and malignant breast lesions. The  
193 challenge remains how to effectively incorporate this model into everyday oncology.

194 **Bayesian ML** algorithms calculate probabilities for hypotheses. The class having maximum probability  
195 is assigned as the most suitable class.[17] A study presented a method for classifying electrocardiogram  
196 (ECG) data into four emotional states according to the stress levels using naive Bayes and SVM  
197 algorithms with the average accuracy of the stress classification of 97.6%. Ability to quantify the stress  
198 signals could facilitate a more effective management of mental state.[36] A Bayesian ML model was  
199 designed to estimate the probability of an individual having an oral Human Papilloma Virus (HPV)  
200 infection, given Oropharyngeal Squamous Cell Carcinomas (OPSCC) and other covariate  
201 information.[37] The model is then inverted using Bayes' theorem to reverse the probability relationship.  
202 The authors analyzed 8,106 OPSCC patients and achieved the AUROC of about 0.7. The Bayesian model  
203 could be utilized to identify risk factors in estimating the probability of medical conditions.

204 **Support Vector Machine** models apply an optimization problem that attempts to find a separating  
205 hyperplane with as large a margin as possible.[18] SVM was trained on 318 samples to distinguish  
206 neurodegenerative movement disorders such as Parkinson's Disease (PD) from healthy subjects, and  
207 from other movement disorders (precision  $\approx$ 81% and recall  $\approx$ 89%).[38] In this study, DNN and RF were  
208 applied to the same task, with DNN achieving the best results. Models were trained on retrospective data  
209 at a single site, with high data quality and none of the different classifiers outperformed the others, which  
210 are some of limitations of these models. SVM models have also been used for diagnosis of early breast  
211 cancer using PET images (116 samples, accuracy up to 85%, AUROC 0.89),[39] and detection of atrial  
212 fibrillation (AF) using ECG data (79 AF and 336 non-AF cases, accuracy 97-100%).[40] Both models  
213 use images as inputs. These models must be tested on bigger data and compared to deep learning since  
214 recent literature show that deep learning models yield better prediction than SVM models on imaging  
215 data.

216 **The K-Nearest Neighbors** algorithm takes into account k-neighboring points when classifying a data  
217 point and assigns the class by finding the most prominent class among the k-nearest data points.[19]  
218 Hepatocellular carcinoma (HCC) dataset from the UCI machine learning repository was used to test  
219 different algorithms, including k-NN classifier, for feature selection and classification. The best results  
220 achieved up to 84% accuracy.[41] The k-NN and SVM classifiers were utilized to determine whether  
221 the patients have abnormal or normal respiration, or have bradypnea (slow breathing), or tachypnea (fast  
222 breathing). The testing accuracies of the completely built SVM and k-NN classifiers were 96% and 99%,  
223 respectively.[42] Constructed models must be tested on more datasets from other institutions to  
224 determine reproducibility of the models. K-NN models have not been used very often for medical  
225 predictions in the last few years.

226 **A Linear Regression** algorithm performs a regression task and predicts a specific value based on an  
227 independent variable.[20] A linear model was created to predict the impact of the duration of exposure  
228 (number of days) to COVID-19 on mortality rates (more than 270,000 patients).[43] Multiple regression  
229 and LR analysis were successfully applied to predict the number of weekly deaths due to COVID-19 in  
230 India (606 patients).[44] LR models are good options for time to event type of predictions and for  
231 predictions of the exact numbers of patients, or the cost of care.

232 **Logistic Regression** uses the logistic function to binary classification and estimates the probability of  
233 the event.[21] Multivariate LogR (as well as RF and XGBoost) models were applied for prognosis of  
234 mortality risk in patients with COVID-19 (292 patients, AUROC  $\approx$ 0.95).[45] The model needs to be  
235 tested on larger multi-center data. A study investigated the application of LogR and RNN LSTM models  
236 in capturing clinical risk factors for outcome prediction of 575 patients with aneurysmal subarachnoid  
237 hemorrhage (AUROC 0.89).[46] Since, the LSTM RNN model achieved higher accuracy, it is likely a  
238 better choice in this type of study. A logistic regression-based ML prognostic algorithm is implemented  
239 in real-time as a clinical decision support (CDS) system to facilitate decision making for patients with

240 suspected COVID-19 in the emergency department (ED). Training data included 1,469 adult patients  
241 who tested positive for Severe Acute Respiratory Syndrome (SARS) within 14 days of acute care. The  
242 algorithm performed well with an AUROC of 0.85.[47] A LogR based ML-enabled CDS can be  
243 developed, validated, and implemented with high performance across multiple hospitals while being  
244 equitable and maintaining performance in real-time validation.

## 245 **Deep learning**

246 **Deep Neural Networks.** DNN is a multilayer neural network with an input layer, hidden layers, and an  
247 output layer. DNN learns weights so the output from the network correctly classifies the example. The  
248 back propagation algorithm is a standard approach to train DNNs.[22] A compartmental model enhanced  
249 with deep learning methodology predicted the dynamics of the COVID-19 epidemic in the U.S. using  
250 the JHU CSSE data repository.[48] The model predicted the number of active cases between 3.2-3.3  
251 million on August 16-18, 2020. The actual number of infected cases on August 16-18, 2020, was about  
252 2.5 million (CDC data), so the model was not accurate. DNN methods were designed, to predict the  
253 dynamics of the COVID-19 pandemic outbreak on JHU CSSE data and Korea Centers for Disease  
254 Control and Prevention data.[49] Predictions of different aspects of COVID-19 epidemic are popular,  
255 but considering the current state of the pandemic, it is difficult to confirm that these models work  
256 accurately in reality. A DNN was designed for prediction of behavior of engineered RNA elements  
257 capable of detecting small molecules, proteins, and nucleic acids.[50] This work shows that DNN  
258 approaches could be used for predictions in RNA synthetic biology, but more data are needed for the  
259 training of DNNs, as well as improvement of DNN architectures. A DNN performed an automatic  
260 diagnosis of the 12-lead ECG recordings and outperformed cardiology residents in recognizing six types  
261 of abnormalities, with F1 scores above 80% and specificity over 99%.[51] Additional studies could test  
262 whether DNN effectively diagnose different ECG abnormalities, including myocardial infarction. DNN,  
263 RF, and a simple statistical test were used to predict COVID-19 infections from full blood counts only

264 (598 samples), without knowing the history of the patients (accuracy up to 91%).[52] It appears that  
265 these DNN models are more of a theoretical work at this stage of development, without evident clinical  
266 implementation. A deep ML model was developed for automatic detection of brain metastases that uses  
267 contrast-enhanced and non-enhanced CT images as inputs. The dataset contained CT scans of 116  
268 patients with brain metastases (total of 659 metastases). Single-shot detector (SSD) ML models were  
269 constructed with a feature fusion module. The sensitivity was 88.7% for the model that used both  
270 contrast-enhanced and non-enhanced CT images (the CE + NECT model) and 87.6% for the model that  
271 used only contrast-enhanced CT images (the CECT model).[53] The model is a contribution to imaging-  
272 based diagnostics, and it needs further testing on larger datasets to improve generalization. Another study  
273 proposed a novel deep learning architecture involving combinations of CNN layers and RNN layers that  
274 can be used to perform segmentation and classification of five cardiac rhythms based on ECG recordings.  
275 The algorithm is developed in a sequence to sequence setting where the input is a sequence of five second  
276 ECG signal sliding windows and the output is a sequence of cardiac rhythm labels. Experimental result  
277 shows this approach can achieve an average F1 scores of 0.89.[54]

278 **Convolutional Neural Networks** use a special kind of linear mathematical operation called convolution.  
279 The hidden layers of a CNN typically consist of a series of convolutional layers.[22] CNNs showed great  
280 potential for melanoma subtypes and localization diagnosis on dermoscopic image datasets (780 images)  
281 and achieved AUROC  $\approx 0.93$ . [55] Improvements in the accuracy of this model could be achieved by  
282 adding more training images of mucosal and subungual sites. Data-augmentation deep models  
283 (DADLM) that enhance the learnability of CNNs and Convolutional LSTM (ConvLSTM) deep learning  
284 models, improve the accuracy of COVID-19 detection.[56] The study used 50 images (X-ray and CT).  
285 This model needs more reliable data to confirm its performance. The fast-track COVID-19 classification  
286 network (FCONet) was developed to diagnose COVID-19 pneumonia in CT images (3,993) and  
287 differentiate it from non-COVID-19 pneumonia and non-pneumonia diseases with  $\approx 99\%$  accuracy.[57]

288 A CNN was also utilized to classify solid, lipid-poor, contrast enhancing renal masses using enhanced  
289 CT images (143 patients) with the accuracy  $\approx 99\%$ , and AUROC  $\approx 0.82$ , [58] and for automated prediction  
290 of breast cancer risk on 92 histopathological images where the F1 score was 0.73. [59] These CNN  
291 models are examples of deep learning that rely on medical imaging. More research that uses EHR, or  
292 medical text data in addition to imaging could contribute to faster and cheaper diagnostics. Transfer  
293 learning is applied to train ResNet-50 and ResNet-101 deep learning models on augmented HAM10000  
294 datasets, which contained about 42,000 dermoscopy skin cancer images. Achieved accuracy was better  
295 when used augmented dataset compared to the original dataset and it was about 91.7%. [60] CNN model  
296 has shown great success in decoding motor preparation of upper limbs from time-frequency maps of  
297 EEG signals. [61] A deep learning architecture was applied to early diagnosis of glaucoma (301 images,  
298 AUROC 0.92), [62] and for early diabetic retinopathy detection, [63] on retinal fundus images (40 images,  
299 AUROC 0.94). Further studies with larger datasets, adding post-processing methods, and improved  
300 optimized deep ML architectures could increase the accuracy of these models. An interpretable  
301 classification approach of ultrasound images for the risk assessment and stratification of patients with  
302 carotid atheromatous plaque was designed using CNNs and achieved AUROC of 0.73. [64] The  
303 integration of interpretability methods with deep learning strategies can facilitate the identification of  
304 ultrasound image biomarkers for the stratification of patients with carotid atheromatous plaque. A dataset  
305 of 1,900 chest X-ray images has been used with the proposed CNN based model: “C19D-Net” to detect  
306 COVID-19 with the accuracy of 96.24%. [65] The idea is to employ the constructed CNN ML model to  
307 help radiologists improve their accuracy of detection of COVID-19 from X-ray images.

308 **Recurrent Neural Networks** are a type of neural networks that allow analysis of temporal heterogeneous  
309 medical data. LSTM or GRU units effectively model the irregular visiting patterns in the long,  
310 heterogeneous sequence of events in EHR. [23] RNNs and the magnetic induction system were integrated  
311 to detect a wide range of human motions. [66] The benefit of LSTM RNN for sequence classification is

312 the ability to support multiple parallel temporal input data from different sensor modalities.[66] LSTM  
313 and GRU RNN models were developed to predict complications of DM2 (two million patients with DM2  
314 diagnosis), with the prediction accuracy up to 84%. They outperformed traditional ML models in  
315 prediction accuracy of 10 selected complications of DM2.[67] An RNN approach was used for predicting  
316 hemoglobin levels in patients with end-stage renal disease (7,739 patients) and produced mean absolute  
317 error (MAE) of 0.54.[68] Further research is needed to incorporate the dialysis and laboratory  
318 information. RNNs were designed for monitoring of depth of anesthesia based on features of EEG signals  
319 (20 patients).[69] LSTM RNN models predicted AD from conditions, measurement, and drugs domain  
320 on about 2,600 patients. A successful application of the drugs domain in prediction of AD was presented  
321 (area under the precision recall curve (AUPRC) 0.99).[70] Additional research with the drugs domain is  
322 required to develop comprehensive clinically applicable ML solutions. Another study utilized arterial  
323 waveforms recorded on 18,813 patients during noncardiac surgery to predict short-term intraoperative  
324 hypotension. A weighted average hybrid of deep learning CNN and RNN models performed the best  
325 (AUPRC 0.716).[71] Intraoperative hypotension has an adverse impact on postoperative outcomes and  
326 accurate prediction could improve survival. Acute kidney injury (AKI) is associated with poor patient  
327 outcomes and increased health care costs. Two RNN algorithms were created using a dataset of more  
328 than 72,000 patients.[72] Model 1 predicted the occurrence of AKI within 7 days with AUROC of 0.84  
329 and model 2 predicted the future trajectory of creatinine values up to 72 hours with AUROC of 0.9.  
330 Further development of the suggested approaches could incorporate the model into CDS systems for  
331 prediction of in-hospital AKI.[72] Researchers leveraged a big dataset (48,151 patients) to build an RNN  
332 to predict the risk of developing hepatocellular carcinoma (HCC). RNN models achieved AUROC of  
333 0.759.[73] Deep learning RNN models outperformed traditional models, suggesting that RNN models  
334 could be used to identify high risk of developing HCC. The performance of the presented RNN models

335 could be improved by training them on better quality hospital datasets and further optimization of deep  
 336 learning models. We summarized the reviewed ML models in Table 2.

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ML Method	Author and year	Topic	
DT	Soguero-Ruiz C, et al 2020	Diabetes Mellitus, Hypertension	24
DT, SVM	Joloudari JH, et al 2020	Coronary artery disease	25
DT	De Felice F, et al 2020	Rectal cancer	26
RF	Chavan S, et al 2020	Liver toxicity	27
RF	Tracy BM, et al 2020	Hernia repair	28
RF	Mar J, et al 2020	Dementia, Neuropsychiatric symptoms	29
RF, AdaBoost	Iwendi C, et al 2020	COVID-19	30
Ensemble bagging	Munteanu CR, et al 2021	Glioblastoma, drugs	31
Ensemble, bagging	Nikolaidis A, et al 2020	Functional parcellation of the human brain	32
Ensemble, AdaBoost	Li S, et al 2020	Colorectal cancer	33
MLP	Car Z, et al 2020	COVID-19	34
MLP	Leithner D, et al 2020	Breast cancer	35
Bayesian, SVM	Kang M, et al 2021	Electrocardiogram signals, Mental stress	36
Bayesian	Tewari P, et al 2021	Oropharyngeal cancer	37
SVM, DNN	Varghese J, et al 2020	Movement Disorders	38
SVM	Satoh Y, et al 2020	Breast cancer	39
SVM	Lown M, et al 2020	Atrial fibrillation	40
K-NN, Boosting, SVM, DT	Angelis I, et al 2021	Hepatocellular cancer	41
K-NN, SVM	Jagadev P, et al 2020	Respiration rate (breathing)	42
LR	Verma V, et al 2020	COVID-19	43
LR, Multiple regression	Ghosal S, et al 2020	COVID-19	44
LogR	Ma X, et al 2020	COVID-19	45
LogR	Tabaie A., et al 2020	Aneurysmal Subarachnoid Hemorrhage	46
LogR	Lupei MI, et al 2022	COVID-19	47
DNN	Deng Q 2020	COVID-19	48
DNN	Jung SY. Et al 2020	COVID-19	49
DNN	Angenent-Mari NM, et al 2020	Genetics	50
DNN	Ribeiro AH, et al 2020	ECG diagnosis, Heart diseases	51
DNN, RF	Banerjee A, et al 2020	COVID-19	52
DNN	Takao H, et al 2021	Brain metastases	53
DNN, CNN, RNN	Pokaparakarn T, et al 2021	ECG Cardiac Rhythm	54
CNN	Winkler JK, et al 2020	Melanoma	55
CNN, DNN, LSTM	Sedik A, et al 2020	COVID-19	56
CNN, DNN	Ko H, et al 2020	Chest CT Image, Pneumonia	57
CNN, DNN	Oberai A, et al 2020	Renal tumor, CT scan	58
CNN, DNN	Wetstein SC, et al 2020	Breast tumors	59
CNN	Arshad M, et al 2021	Skin cancer	60
CNN	Mammone N, et al 2020	EEG signals, Motor upper limb	61
CNN	Muramatsu C. 2020	Glaucoma, Retinal fundus images	62
CNN, DNN	Hatanaka Y. 2020	Retinopathy	63
CNN	Ganitidis T, et al 2021	Carotid artery stenosis, Ultrasound	64
CNN	Kaur P, et al 2021	COVID-19	65
RNN	Golestani N, et al 2020	Human activity recognition	66
RNN, RF, MLP	Ljubic B, et al 2020	Diabetes mellitus, complications	67
RNN	Lobo B,	End-Stage Renal Disease, Hemoglobin	68
RNN	Li R, et al. 2020	Monitoring Depth of Anesthesia	69
RNN LSTM	Ljubic B, et al 2020	Alzheimer's disease	70



RNN	Choe S, et al 2021	Hypotension (intraoperative)	71
RNN	Kim K, et al 2021	Acute Kidney Injury	72
RNN	Ioannou GN, et al 2020	Hepatocellular cancer	73

339

340 Table 2. Reviewed articles, classified by ML model types. First authors, publication year, and medical  
341 topics described in the publications.

342

343

344 The number of articles by types of medical conditions and topics is presented in Table 3.

345

Types of diseases by systems or therapy	Number of reviewed articles
Neoplasms (Oncology)	13
Nervous System and Sense Organs	12
COVID-19	11
Circulatory System	10
Endocrine, Nutritional and Metabolic	2
Respiratory System	2
Genitourinary System	2
Mental Disorders	2
Digestive System	1
Surgical procedures	1
Genomics, proteomics	1
New drugs, drug therapy	1

346

347 Table 3. The number of analyzed articles by types of medical conditions.

348

## 349 **DISCUSSION**

350 This review shows that most ML models in medicine represent great software solutions with high  
351 prediction accuracy, but only handful of models could find an implementation in medical practice.

352 Neurological conditions are among the most common medical system subject to ML model  
353 applications.[29,31,32,38,46,53,61-63,66,69,70] The most frequent type of data used in these

354 applications were imaging data. Images consist of spatially coherent pixels in a local region, meaning  
355 that pixels close to each other share similar information. Deep learning architectures (especially CNN)

356 produce higher accuracy predictions from image inputs than from EHR type of datasets, which are often  
357 heterogeneous. Another medical discipline extensively used in ML analysis is oncology. Accurate



358 predicting the development of cancers or complications of cancers could indicate earlier diagnosis and  
359 therapeutic approaches that would improve outcomes. [26,31,33,35,37,39,41,53,55,58-60,73] The  
360 majority of these ML applications use imaging data (most often histologic type) for classification of  
361 malignant versus benign tumors. Cardiovascular conditions and DM are among the most common  
362 medical conditions used in predictive analysis. [24,25,36,40,46,51,54,64,67,71] The challenges with  
363 these types of predictions are often related to limitations of data availability. Insurance claims data was  
364 frequently used but often lacks important clinical information such as laboratory results and  
365 medications.[67,70]

366 Many traditional and deep ML models were utilized with the goal of helping to detect COVID-19  
367 infections, complications, or outcomes as one of the most frequent research topic in the last two years.  
368 [30,34,43-45,47-49,51,52,56,65]

369 The performance of predictive ML models in medicine depends on multiple factors. For challenging  
370 prediction problems, the understanding of disease is likely to lead to more accurate prediction. Physicians  
371 must be better motivated to use ML developments, which is not always easy to achieve since they  
372 perceive this activity as something that decreases their time with patients.[1] Since many physicians use  
373 computers daily, better presented benefits of ML prediction models could increase their adoption in  
374 medicine. Evidence-based medicine requires statistical analysis of medical data and ML is a form of that  
375 analysis. Some form of ML should become a part of statistics teaching in medical school to prepare  
376 future physicians for meaningful adoption of medical ML models. To make ML more meaningful in  
377 clinical practice, we should focus on tasks that physicians need help with and where results of ML could  
378 help physicians to improve their decisions. The computers that physicians use for EHR could also be  
379 used for ML models. Additionally, ML is relatively inexpensive compared to basic science and large-  
380 scale clinical research.

381 Traditional ML methods do not always achieve accuracy that would convince medical doctors of the  
382 benefits of the proposed predictive models.[24-47] A prediction accuracy of 70-90% is generally a good  
383 result in terms of performances of ML models but may not be high enough to suggest clinically  
384 meaningful improvements in practice. Traditional models have the advantage of simplicity and  
385 interpretability but suffer from somewhat worse accuracy.[38,52,67]

386 The most successful and meaningful application of deep learning ML models was achieved in the  
387 imaging field.[53,55-65] Analyses of CT scans, X-rays, Doppler ultrasound, histo-pathological images  
388 obtained high accuracy results, which often outperform medical experts. RNN models capture the  
389 temporal nature of EHR, imaging and other medical data to predict diseases, complications, and  
390 outcomes.[66-73] Deep learning models produce higher accuracy but suffer from issues of  
391 interpretability and instability.[15,75] Combinations of traditional and deep learning models could  
392 address challenges of interpretability and accuracy.[38,52,67] Many datasets are small and do not have  
393 enough samples for implementation of deep learning models. In those cases, traditional ML models are  
394 the only option.

395 To build effective ML models, we must understand how to select relevant features to train ML models.  
396 Computational methods that use optimization function to automatically select useful features have been  
397 developed.[76,77] In addition to automatically selected features, we often use medical domain  
398 knowledge to identify useful features that could help in improvement of predictions.[67,70] If analyses  
399 point toward certain features as the most important for obtaining the model performance, the next  
400 challenge is how to quantify the relevance of those features.

401 An important dilemma is the selection of the most optimal ML models for a specific task. We need to  
402 consider which specific medical problem we want to solve. We must also determine how much and what  
403 type of data are available, how much data are missing, and whether temporal information is included.  
404 Implementation of ML in prediction of medical conditions using EHRs and other non-imaging data as

405 cheaper source of data could achieve meaningful results at lower cost. We would need to weigh positive  
406 and negative factors in each of the options before we select the most optimal model for the given task.  
407 Predictive ML models could potentially help to build CDS systems to make better medical decisions.  
408 These models can provide recommendations to select suitable patients for clinical trials.[70] Domain  
409 knowledge and collaborations between physicians and ML experts can improve the prediction  
410 performance of ML models in medicine and facilitate implementation in clinical practice. Prediction ML  
411 models could help clinicians to select the most effective diagnostic and therapeutic choices available.  
412 Successful ML models can make medicine more efficient, improve outcomes, and decrease medical  
413 errors. We predict that ML models will continue to develop, and they will be applied more broadly in  
414 clinical practice.

415

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## 422 **AUTHORS CONTRIBUTORSHIP**

423 BL, MP, AG, DR, GC, and Z.O. performed the literature review and wrote the paper.

424 The authors have no competing interests to declare.

425

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