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Machine-learning-based analysis of the sensitivity and specificity on lipid-lowering effect of one-month-administered statins

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Abstract

Few predictive studies have been reported on the efficacy of atorvastatin in reducing lipoprotein cholesterol to be qualified after 1-month course of treatment in different individuals. A total of 14,180 community-based residents aged ≥ 65 received health checkup, 1013 of whom had low-density lipoprotein (LDL) higher than 2.6mmol/L so that they were put on 1-month course of treatment with atorvastatin. At its completion, lipoprotein cholesterol was measured again. With < 2.6 mmol/L considered as the treatment standard, 411 individuals were judged as the qualified group, and 602, and as the unqualified group. The basic sociodemographic features covered 57 items. The data were randomly divided into train sets and test ones. The recursive random-forest algorithm was applied to predicting the patients response to atorvastatin, the recursive feature elimination method, to screening all the physical indicators. The overall accuracy, sensitivity and specificity were calculated, respectively, and so were the receiver operator characteristic curve and the area under the curve of the test set. In the prediction model on the efficacy of 1-month treatment of statins for LDL, the sensitivity, 86.86%; and the specificity, 94.83%. In the prediction model on the efficacy of the same treatment for triglyceride, the sensitivity, 71.21%; and the specificity, 73.46%. As to the prediction of total cholesterol, the sensitivity, 94.38%; and the specificity, 96.55%. And in the case of high-density lipoprotein (HDL), the sensitivity, 84.86%; and the specificity, 100%. recursive feature elimination analysis showed that total cholesterol was the most important feature of atorvastatin efficacy of reducing LDL; that HDL was the most important one of its efficacies of reducing triglycerides; that LDL was the most important one of its efficacies of reducing total cholesterol; and that triglyceride was the most important one of its efficacies of reducing HDL. Random-forest can help predict whether atorvastatin efficacy of reducing lipoprotein cholesterol to be qualified after 1-month course of treatment in different individuals.

Abbreviations: AUC = area under the curve, Aβ = Amyloid β, CVD = cerebrovascular disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RFE = recursive feature elimination.

Keywords: algorithms, atorvastatin, lipid, machine-learning, screening

1. Introduction

Cerebrovascular disease (CVD) and in particular stroke account for the largest proportions (47%–67%) of total disability-adjusted life-years and deaths among all the common neurological disorders worldwide.[1]CVD can induce cognitive impairment, of which the prevalence of major poststroke dementia ranges from 7% to 67.3%, and currently no definitively proven pharmacologic therapies are available for recovery from poststroke cognitive impairment and vascular dementia.[2,3] Additionally, CVD can evoke poststroke epilepsy, which accounts for nearly 50% of newly diagnosed epilepsy in the patients aged > 60.[3,4] It is well recognized that, therefore, cerebrovascular disease is a serious disease that endangers human health.

Statins, such as atorvastatin, which have been convincingly proved to be associated with a reduction in the absolute risk of ischemic strokes and cardiovascular events, have modest differences in efficacy, signaling potential therapeutic equivalence.[5–9]It was confirmed that atorvastatin ameliorated the defects in sensorimotor behaviors and reduced microglia-mediated neuroinflammation by inhibiting proinflammatory polarization of microglia in the peri-infarct cortex of the mice with permanent middle cerebral artery occlusion. Atorvastatin was once reported to effectively reduce the expression of toll like receptor 4 and NF-κB in the brain tissue, having a certain protective effect on cerebral

HL and RJ contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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nerve function, which could be expected to be the first therapeutic choice for a stroke, and it could reduce the incidence of epilepsy after a stroke by inhibiting inflammation.[10] Moreover, statins were thought to reverse microvascular dysfunction and reduce neuroinflammation during sepsis, preventing the development of long-term cognitive decline.[8,11]Thus, it is important that atorvastatin therapy be administered to reduce blood lipids to a low risk level of vascular disease.

But idiosyncratic liver injury due to statins has been reported to affect the patients by 1.9% to 5.5% in the prospective series of drug-induced liver injury, and such a damage was associated with the dose and duration of treatment with satins.[12,13] The statin treatment induced approximately 1.5% to 5.0% of the patients who experienced adverse muscular symptoms.[14] Of note, a long-term high dose of atorvastatin administration could lead to a reduced rate in compliance.[15]Therefore, adequate atorvastatin treatment can reduce the chance of liver damage by bringing the lipid level up to standard as soon as possible, since the low dose of atorvastatin can be maintained for a long time. It is well known that the efficacy of statins depends on many factors[15]; however, few predictive studies have been reported on the efficacy of statins administered for a 1-month course of treatment for lipid reduction in individuals. Our study was to predict, using supervised machine-learning, the lipid-lowering effect of atorvastatin in the 1-month course of treatment in individuals.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Medical Ethics Committee of Shanghai Pudong New Area People's Hospital, Shanghai, China (Prylz-2020-085). Written informed consent was obtained from all participants or their legally acceptable representatives.

2.2. Subject recruitment

From May 1, 2021 to December 31, 2021, for the study all subjects were chosen from the local community-based residents aged ≥ 65 without the clinical history of statins, for whom had been provided free health checkup as the welfare of the local government. Those were excluded who had taken statins, or who had abnormality in the function of the liver/kidney or in muscle enzyme, as indicated in Figure 1.

2.3. Lab examination

In the current study, the blood routine indexes were listed as follows: lymphocyte count, percentage of monocyte, percentage of basophils, eosinophil count, hemoglobin, hematocrit, platelet distribution width, red blood cells, percentage of neutrophils,

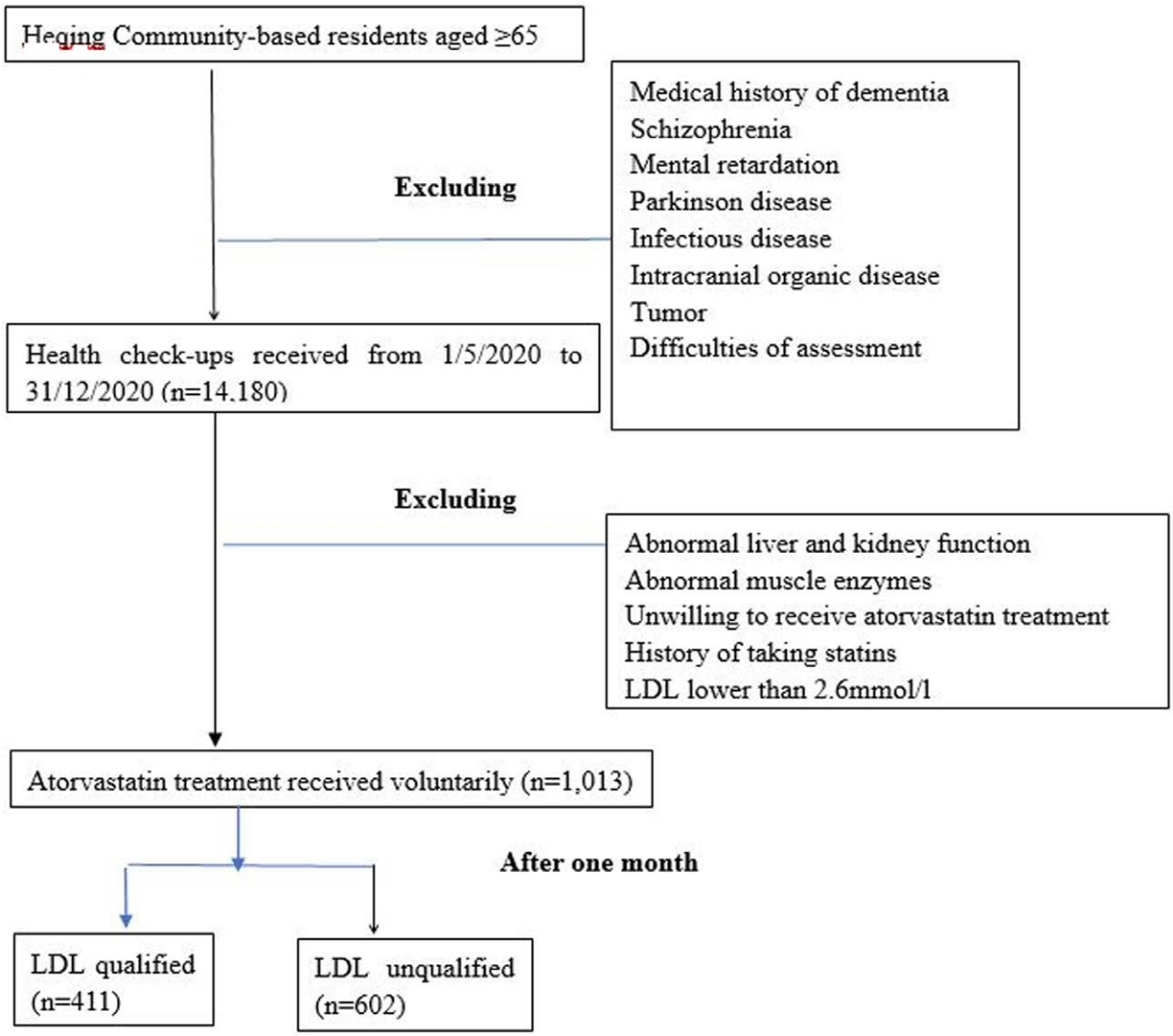

Figure 1. The flow chart of the individuals recruited and tested.

mean corpuscular volume, and red cell distribution width and platelets. A routine analysis of blood tests was performed using Sysmex XT-4000i (Japan). The cut off value for red cell distribution width was 39 to 46FL.

From all participants was collected whole blood after overnight fasting using venipuncture, 4mL of blood collected into anticoagulant tube (BD vacutainer), which was to be kept for 1 hour at room temperature (RT), and before centrifuged at 1000g for 10 minutes at RT. The resultant supernatant (serum) was divided into 2 Eppendorf tubes (1mL each) to be temporarily stored at -80°C until examination. For this study 8 components were selected such as Amyloid β (Aβ)1-40, Aβ1-42, P-tau, preprandial blood glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol and triglyceride.

The enzyme-linked immunosorbent assay-based techniques was used to assess serum Aβ1-40/Aβ1-42/P-tau. The serum levels of Aβ1-40 (Cat. No: DAB140B; Sensitivity: 1.31–8.17pg/mL), Aβ1-42 (Cat. No: DAB142; Sensitivity:0.762–4.73pg/mL) were quantified using a commercial enzyme-linked immunosorbent assay kits (R&D Systems, MN) according to the manufacturer's protocol. P-tau (Cat. No: CSB-E17929h; Sensitivity:<7.8pg/mL). The concentrations of serum HDL/LDL/preprandial blood glucose were determined by a Cobas C501 automatic biochemistry analyzer using the enzymatic conversion method. The kit was supplied by Roche Diagnostics GmbH (Mannheim, Germany).

2.4. Collection of other clinic features

All subjects were registered or tested for the personal information pertaining to age, gender, height, weight, education level and hypertension, smoking, drinking, liver ultrasound, heart rate, physical exercise, EEG, eyesight, etc, the total number of items reaching 57 (Table 1).

2.5. Statistical analysis

The version 19.0 of Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) was applied to the current statistical analysis. Descriptive statistics was used to calculate by percentage the sociodemographic characteristics of the participants; the chi-square test, to assess the differences between different subgroups in terms of gender, smoking, hypertension history, rhythm, urine leukocyte, hematuria, urobilinogen, urine protein, urine microcreatinine, urine Vitamin C, nitrite; and *t* test, to assess the measurement data.

2.6. Random-forest algorithm

All data were randomly split into the training and test set based on the random-forest algorithm on Python (70% vs 30%).Recursive random-forest algorithm was used for supervised machine-learning.[16,17] In the multivariate regression model to predict the patients response to atorvastatin, the basic features were screened out using recursive feature elimination (RFE), and a calculation was made of the overall accuracy, sensitivity and specificity, receiver operating characteristic curves and areas under the curve (AUC) of the test set.

Based on the all features, we began to establish the predicting model so that we could predict the lipid-lowering effect of atorvastatin prescribed as a 1-month course of treatment. We judged the superiority of the model in terms of accuracy, sensitivity, specificity and AUC. Afterwards, and through RFE we made an analysis of the significant features. Random-forest algorithm was implemented based on Anaconda which is Python-based data science platform.

3. Results

A total of 1013 people aged ≥ 65 were assessed to meet the inclusion and exclusion criteria before accepting the prescription of atorvastatin at 20mg QN. One month later, of 1013 subjects, 411 and 602 fell under the qualified and unqualified group, respectively; and a list was made of their basic features (Table 1).

3.1. The predicting model for the efficacy of a 1-month course of statins treatment on lipoprotein cholesterol

As indicated in the predicting model on LDL, the training accuracy of random-forest was 100%; the correct rate of test, 91.80%; the sensitivity, 86.86%; and the specificity, and 94.83%, with AUC = 0.97. According to the observation made on the importance of the basic line features as the variables of the predicting model on LDL, the random-forest algorithm sorted out an order, as indicated in Figure 2A, with the top 3 factors affecting the rapid LDL-lowering effect of statins such as total cholesterol, triglyceride and blood platelet count.

From the predicting model on triglyceride, the training accuracy of random-forest was 100%; the correct rate of test, 71.7%; the sensitivity,71.21%; and the specificity, 73.46%, and with AUC = 0.80. This sorted our order, as indicated in Figure 2B, with the top 3 factors affecting the rapid triglyceride-lowering effect of statins such as HDL, LDL and total cholesterol.

In predicting total cholesterol, the training accuracy of random-forest was 100%; the correct rate of test, 94.90%; the sensitivity, 94.38%; and the specificity, 96.55%, and with AUC = 0.98. As indicated in Figure 2C, an order was thus sorted out, with the top 3 factors affecting the rapid total cholesterol-lowering effect of statins such as LDL, triglyceride and HDL.

In predicting HDL, the training accuracy of random-forest was 100%; the correct rate of test, 86.04%; the sensitivity, 84.86%; the specificity, 100%, and with (AUC = 0.87). From this, an order was sorted out, as indicated in Figure 2D, with the top 3 factors affecting the rapid HDL-lowering effect of statins such as triglyceride, weight and uric acid.

3.2. The specific correlation of the first fifteen features in different models

According to the linear regression analysis of the first fifteen features in different models (Table 2), it was discovered that LDL was positively associated with total cholesterol and blood platelet, but was negatively linked with HDL, triglyceride and red blood cell distribution width; that triglyceride was positively associated with total cholesterol and uric acid, but was negatively linked with HDL and creatinine; that total cholesterol was positively associated with HDL; and that HDL was positively associated with hipline, but was negatively linked with weight ($P < .05$).

4. Discussion

In our study, we chose random-forest algorithm to predict the efficacy of atorvastatin in reducing lipid to be qualified after 1-month course of treatment in different individuals, from which we found the prediction model was effective. In the predicting model to predict the efficacy on LDL, the important factors were observed to be total cholesterol, and triglyceride and blood platelet count. A previous study found that platelet count was correlated with plasma-LDL cholesterol, that platelets stored and released PCSK9 (pltPCSK9) upon activation, which was enhanced in the presence of LDL.[18] In the current predicting model to predict the efficacy on triglyceride, the important factors were referred to as HDL, LDL and total cholesterol. It was previously reported the triglyceride and HDL were closely

Table 1

The basic line features of 2 groups.

Features	Qualified group (N = 411)	Unqualified group (N = 602)	F/χ^2	P
Education	4.06 ± 3.01	4.08 ± 2.88	9.08	.92
Age	73.76 ± 6.10	73.15 ± 5.91	0.85	.11
weight	63.04 ± 11.52	62.66 ± 10.99	1.20	.59
Systolic pressure	151.32 ± 19.40	154.71 ± 19.48	0.01	.07
Diastolic pressure	84.13 ± 10.55	87.20 ± 10.50	0.00	<.001
Daily alcohol consumption	22.02 ± 7.32	17.03 ± 6.80	4.58	.26
LDL	3.78 ± 1.66	3.79 ± 5.82	0.73	.70
Triglyceride	2.32 ± 0.80	2.83 ± 0.88	15.46	<.001
HDL	2.57 ± 0.39	2.54 ± 0.35	5.04	.21
Total cholesterol	4.16 ± 0.60	5.68 ± 0.75	23.06	<.001
Carcinoembryonic antigen	2.48 ± 1.66	2.59 ± 5.82	0.71	.72
Red blood cell distribution width	46.91 ± 3.72	45.65 ± 2.84	15.44	<.001
Red blood cell	4.29 ± 0.47	4.40 ± 0.42	3.78	<.001
Hematokrit	0.39 ± 0.03	0.40 ± 0.03	2.82	.008
Lymphocyte ratio	31.80 ± 7.81	34.00 ± 8.08	0.01	<.001
Uric Acid	317.92 ± 89.85	317.86 ± 92.64	0.11	.99
Blood platelet	169.50 ± 56.48	193.25 ± 54.52	0.14	<.001
Mean corpuscular volume	93.25 ± 4.59	92.33 ± 3.64	11.27	<.001
Height	160.85 ± 8.35	159.28 ± 8.31	0.01	.003
Mean hemoglobin	31.91 ± 1.84	31.57 ± 1.52	9.02	.002
Diastolic pressure	84.13 ± 10.55	87.20 ± 10.50	0.00	<.001
Creatinine	74.71 ± 18.76	71.54 ± 18.69	0.75	.008
Carcinoembryonic antigen	2.48 ± 1.66	2.59 ± 5.82	0.71	.72
Urine specific gravity	1.01 ± 0.004	1.01 ± 0.002	0.62	.72
Large platelet ratio	31.72 ± 10.28	29.07 ± 8.57	8.30	<.001
Glutamic-pyruvic transaminase	22.61 ± 19.32	24.07 ± 18.03	0.51	.22
Mean corpuscular volume	83.25 ± 4.59	92.33 ± 3.64	11.27	<.001
Creatinine	74.71 ± 18.76	71.54 ± 18.69	0.75	.008
Lymphocyte ratio	31.980 ± 7.81	34.00 ± 8.08	0.01	<.001
Lymphocyte count	1.89 ± 0.62	2.09 ± 0.65	0.02	<.001
Urine creatinine	143.05 ± 83.25	141.30 ± 80.40	0.99	.74
Urea	6.05 ± 1.71	5.97 ± 1.71	0.03	.46
Urinary microalbumin	67.03 ± 56.31	70.53 ± 56.19	0.05	.34
Mean hemoglobin	31.91 ± 1.84	31.57 ± 1.52	9.02	.002
Mean hemoglobin concentration	342.10 ± 9.07	341.10 ± 9.07	0.18	.76
Mean platelet volume	10.85 ± 1.36	10.45 ± 1.10	12.12	.76
Power of hydrogen	6.15 ± 0.66	6.18 ± 0.67	0.40	.54
Hipline	91.72 ± 7.64	92.09 ± 7.69	0.31	.45
Heart rate	74.36 ± 12.88	74.63 ± 11.89	0.42	.73
Hemoglobin	136.74 ± 13.86	138.82 ± 12.89	1.86	.01
Blood platelet	169.50 ± 56.48	193.51 ± 4.52	0.14	<.001
Platelet distribution width	14.42 ± 3.37	13.58 ± 2.57	15.50	<.001
Waistline	83.99 ± 9.64	83.54 ± 9.39	0.45	.45
Neutral cell ratio	58.14 ± 8.70	56.41 ± 8.62	0.11	.002
Neutral cell number	3.56 ± 1.20	3.55 ± 1.15	2.53	.84
Median cell ratio	10.04 ± 3.02	9.56 ± 2.77	1.68	.008
Median cell count	0.59 ± 0.20	0.58 ± 0.21	0.15	.63
Fasting blood glucose	6.08 ± 1.88	6.01 ± 1.67	3.18	.55
Smoking	73 (18.0%)	87 (14.5%)	2.12	.08
Hypertension	278 (68.1%)	422 (70.6%)	0.67	.22
Rhythm	27 (6.6%)	17 (2.8%)	8.17	<.01
Urine leukocyte	81 (19.7%)	135 (22.4%)	1.07	.31
Hematuria	32 (7.8%)	64 (10.6%)	2.26	.15
Urobilinogen	29 (7.6%)	47 (8.2%)	0.15	.71
Urine protein	77 (20.1%)	119 (20.9%)	0.09	.8
Urine microcreatinine	19 (4.9%)	28 (4.9%)	2.68	.26
Nitrite	22 (5.7%)	25 (4.4%)	0.87	.36
Vitamin C	21 (5.5%)	36 (6.3%)	0.30	.67

HDL = high-density lipoprotein, LDL = low-density lipoprotein.

entangled.[19] By comparison, the important factors were triglyceride, weight and uric acid, as sorted out in the current predicting model. Additionally, body weight appeared to play a role in the decreased HDL-C levels and uric acid impacted the role of HDL-C on carotid atherosclerosis.[20,21]

In fact, the random-forest algorithm has been widely used to diagnose different diseases and predict the outcome of disease, such as machine-learning that was considered to play a role in the prediction of pathological diagnosis of ovarian cancer from preoperative examinations[22]; a CVD prediction model that was applied to 3-year risk assessment of CVD to find that its AUC evaluated the predicting ability to be 0.78[23]; the prostate cancer prediction based on the random-forest algorithm to take into account the transrectal ultrasound findings, ages, and serum levels of prostate-specific antigen[24]; COVID-19 predicting model that used the patients' geographical, traveling, physical

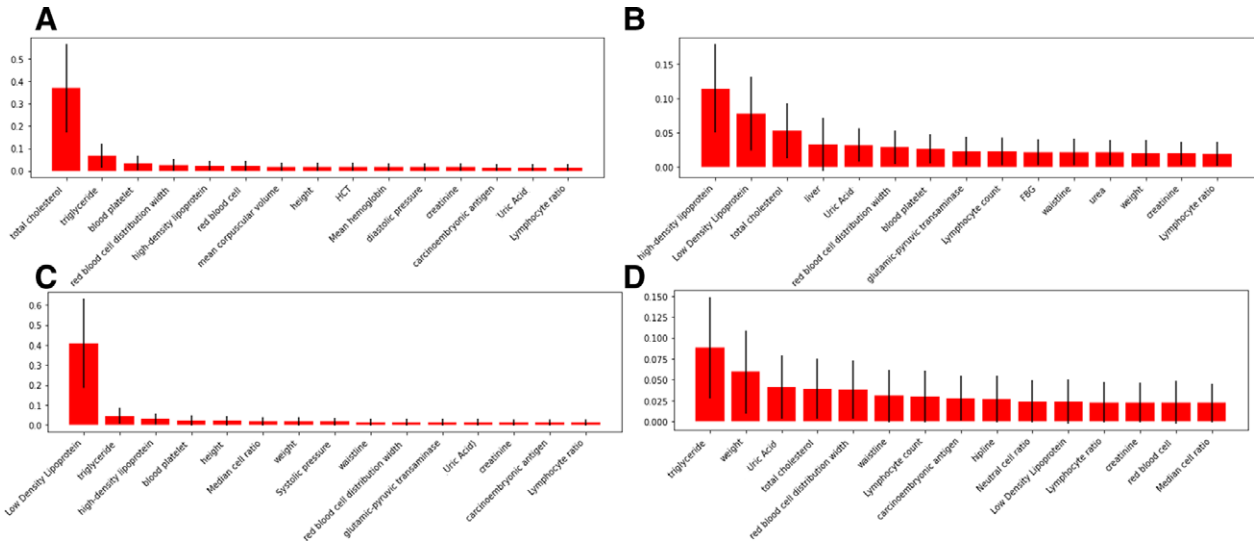

Figure 2. The priority order of features in each predicting model.

Table 2

The linear regression analysis of the first 15 features in different models.

Models	Features	*B*	Beta	*t*	*P*
LDL	Total cholesterol	0.72	1.04	188.80	<.001
	HDL	−0.57	−0.30	−50.80	<.001
	Triglyceride	−0.04	−0.05	−9.94	<.001
	Blood platelet	0.0001	0.01	2.69	.007
	Red blood cell distribution width	−0.002	−0.01	−2.07	.038
Triglyceride	HDL	−1.29	−0.54	−19.67	<.001
	Total cholesterol	0.32	0.37	14.10	<.001
	Lymphocyte count	0.04	0.03	1.37	.169
	Uric Acid	0.001	0.11	3.76	<.001
	Creatinine	−.006	−0.11	−4.04	<.001
Total cholesterol	LDH	1.33	0.92	193.90	<.001
	HDL	0.81	0.29	58.50	<.001
	Triglyceride	0.07	0.06	12.00	<.001
HDL	Triglyceride	−0.11	−0.27	−18.95	<.001
	Total cholesterol	0.91	2.512	53.99	<.001
	LDH	−1.20	−2.29	−48.71	<.001
	weight	−0.004	−0.10	−5.32	<.001
	hipline	0.003	0.05	3.16	.002
	Uric Acid	−0.03	−0.04	−2.89	.004

HDL = high-density lipoprotein, LDL = low-density lipoprotein.

and demographic data to predict the severity of the case and its possible outcome, recovery or death, the accuracy of which was 94%[25]; the machine-learning algorithms that improved the prediction of long-term outcomes in ischemic stroke patients[26]; and the random-forest approach to predict therapeutic efficacy from the data of the failed clinical drug trials so that they could reevaluate the efficacy of the drug.[27]As suggested from the literature, machine-learning has a unique advantage in diagnosis and prediction. In our study, similarly, we found that the predicting ability of this model was relatively high, as indicated in the model to predict the efficacy of 1-month course of statins treatment on LDL, triglyceride, and total cholesterol and HDL.

In our study, we found that triglyceride was positively associated with total cholesterol and uric acid, but negatively linked with HDL and creatinine. Such a finding was consistent with those reported by some other studies,[12,28–31] but not in 1 study where HDL was found to be positively correlated with total triglycerides.[32]

Additionally, we found that HDL was positively associated with total cholesterol and hipline, but negatively associated with body weight, which was not echoed by the evidence that the correlation between HDL and total cholesterol was not significant in Japan and South Korea.[33] In a previously reported study, HDL and hipline were found to be reduced with acupuncture, which indirectly reflected the positively correlation of HDL with hipline,[34] and in another study, increased body weight would impair the protective functions of HDL,[35] and which supported our finding that HDL was negatively associated with body weight.

In the clinic, the treatment of the patients who have acute cerebral infarction needs strong lipid-lowering effect to reach the target of 1.8mmol/L.[36] In our clinic, however, we found that statins did not produce an ideal effect on some patients, and thereby attaching much importance to the pursuit of the influencing factors which affect their rapid lipid-lowering effect. According to our literature review, there has been a dearth of such relevant studies previously reported. As demonstrated by our findings, there were 4 model-based sets of top 3 factors which can affect the rapid LDL-lowering effect of statins: total cholesterol, triglyceride and blood platelet count; HDL,

LDL and total cholesterol; LDL, triglyceride and HDL; and triglyceride, weight and uric acid. With an understanding of the 4 categories of influencing factors, we can better recommend corresponding medications for the patients to ensure the lipid-lowering effect of statins.

5. Conclusions

Random-forest algorithm can help predict whether the efficacy of atorvastatin is qualified in reducing lipid after 1-month course of treatment in different individuals, including the efficacy of reducing LDL and triglycerides and total cholesterol and HDL. RFE of the random-forest algorithm analysis can help list the order of all contributing features to the model construction, which can be explained in terms of their respective correlation in the clinic.

6. Limitation

Although our prediction model was verified to be effective in terms of the main predictive factors detected, the specific cutoff values of some predictive factors were not very exact, such as the HDL value, which surely needs to be further investigated with bigger sample sizes.

Author contributions

Conceptualization: Juan Yang.
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Formal analysis: Fei Feng.
Funding acquisition: Juan Yang.
Project administration: Huiqin Liu.
Supervision: Xiaohui Zhao.
Writing – original draft: Juan Yang.

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