

# Machine Learning-Based Prediction Method for Tremors Induced by Tacrolimus in the Treatment of Nephrotic Syndrome

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#### **OPEN ACCESS**

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#### Reviewed by:

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#### Specialty section:

This article was submitted to Renal Pharmacology, a section of the journal Frontiers in Pharmacology

Received: 12 May 2021 Accepted: 25 March 2022 Published: 27 April 2022

#### Citation:

Shao B, Qu Y, Zhang W, Zhan H, Li Z, Han X, Ma M and Du Z (2022) Machine Learning-Based Prediction Method for Tremors Induced by Tacrolimus in the Treatment of Nephrotic Syndrome. Front. Pharmacol. 13:708610. doi: 10.3389/fphar.2022.708610 Tremors have been reported even with a low dose of tacrolimus in patients with nephrotic syndrome and are responsible for hampering the day-to-day work of young active patients with nephrotic syndrome. This study proposes a neural network model based on seven variables to predict the development of tremors following tacrolimus. The sensitivity and specificity of this algorithm are high. A total of 252 patients were included in this study, out of which 39 (15.5%) experienced tremors, 181 patients (including 32 patients who experienced tremors) were randomly assigned to a training dataset, and the remaining were assigned to an external validation set. We used a recursive feature elimination algorithm to train the training dataset, in turn, through 10-fold cross-validation. The classification performance of the classifer was then used as the evaluation criterion for these subsets to find the subset of optimal features. A neural network was used as a classification algorithm to accurately predict tremors using the subset of optimal features. This model was subsequently tested in the validation dataset. The subset of optimal features contained seven variables (creatinine, D-dimer, total protein, calcium ion, platelet distribution width, serum kalium, and fibrinogen), and the highest accuracy obtained was 0.8288. The neural network model based on these seven variables obtained an area under the curve (AUC) value of 0.9726, an accuracy of 0.9345, a sensitivity of 0.9712, and a specificity of 0.7586 in the training set. Meanwhile, the external validation achieved an accuracy of 0.8214, a sensitivity of 0.8378, and a specificity of 0.7000 in the validation dataset. This model was capable of predicting tremors caused by tacrolimus with an excellent degree of accuracy, which can be beneficial in the treatment of nephrotic syndrome patients.

Keywords: tremor, tacrolimus, nephrotic syndrome, machine learning model, recursive feature elimination, neural network

# INTRODUCTION

Tacrolimus is a profoundly effective immunosuppressive drug that blocks calcineurin-mediated T-cell activation by binding to the immunophilin FKBP12 (Yamauchi et al., 2004). It is used to prevent allograft rejection in solid organ transplantation. In recent years, it has also been widely used for further immunosuppression in immune-mediated glomerular diseases, particularly in steroid-dependent and steroid-refractory nephrotic syndromes (NSs) (Manabe et al., 2018). Clinical applications show that tacrolimus has significant inter- and intra-individual variability in pharmacokinetics and clinical responses. However, tacrolimus treatment is associated with various adverse reactions (ADRs), including acute and chronic nephrotoxicities, neurotoxicities, hypertension, posttransplant diabetes mellitus, gastrointestinal manifestations, and hyperlipidemia (Campagne et al., 2019). Several studies have reported that tacrolimus-related ADRs were more frequent or severe at higher tacrolimus exposures. The frequency and severity of neurotoxicities and several other ADRs have been reduced by adhering to dose minimization protocols for tacrolimus drug exposure after a transplant (Ali, 2013; Campagne et al., 2019).

However, a tremor as a mild neurotoxic manifestation was the most common ADR, affecting 4.5–56% of patients (from SIDER 4.1: Side Effect Resource-http://sideeffects.embl.de/). A reduction in the dosage of tacrolimus is not sufficient to reduce or prevent tremors. Patients have often complained of tremors even during treatment of NS with low doses of tacrolimus (0.05–0.1 mg/kg/d). There are no data on the usage of tacrolimus in the treatment of NS and the consequent occurrence of tremors. The tremors affected both upper and lower limbs and were considered to be induced by movement; however, in approximately 50% of the cases, tremors occurred during movement and rest (Erro et al., 2018). Such tremors significantly affect the work and personal lives of NS patients, and patients would not be able to tolerate tacrolimus treatment.

In recent years, a machine learning model was used to predict the occurrence of ADRs after a drug was administered. This model could obtain the characteristic variables related to the occurrence of ADRs and identify high-risk patients prone to some type of ADRs early on to change treatment strategies (Tangiisuran et al., 2014; van Dijkhuizen et al., 2015; Yin et al., 2017). Studies on tacrolimus-induced tremors are limited, and there are many unanswered questions, especially in cases where tacrolimus was administered in small doses. One study had suggested that the cholesterol plasmatic concentration may play a role in predicting the occurrence of tremors in kidneytransplant patients on tacrolimus therapy, but further research is necessary for verification (Erro et al., 2018). This study presents a good model to assess the predictive factors for tremors induced by tacrolimus therapy for NS patients. At the same time, this study is also the first to use seven variables. The tremors that patients undergoing tacrolimus therapy commonly experience are debilitating, and their prediction can aid in providing better medical treatment to nephrotic syndrome patients.

# MATERIALS AND METHODS

# Patients and Study Design

From January 2013 to December 2017, a total of 341 patients were diagnosed with NS, and they were initially treated with tacrolimus (0.05 mg/kg, the daily dose was not greater than 4 mg, and the blood concentration was not greater than 8 ng/ml). All patients received correct medication instructions and follow-up from clinical pharmacists. The ADRs experienced by the patients, including tremors, were recorded during these follow-ups. Eventually, 252 patients could take tacrolimus for more than 3 months and had more than one follow-up within 6 months. We subsequently performed a retrospective single-center study using the data from the aforementioned patients, which were available on the electronic medical record system at the Second Affiliated Hospital of Harbin Medical University. The detailed demographics and baseline clinical characteristics were collected for further study before the patients were treated with tacrolimus.

## **Ethics Approval and Consent to Participate**

The protocols used in this study were approved by the Medical Ethical Committee of the Second Affiliated Hospital of Harbin Medical University (No. KY 2017-242). All subjects were anonymized, and the ethics committee approved the waiving of informed consent. This study has conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

# Definition

In this study, NS is defined as a group of clinical syndromes, including macroalbuminuria (adult>3.5 g/d), hypoproteinemia (<30 g/L), obvious edema, and/or hyperlipidemia (Nishi et al., 2016).

# **Statistical Analysis**

Continuous variables were presented as mean values with a 95% confidence interval, and the categorical variables were expressed as the number and corresponding percentage of each category (e.g., male). A *t*-test was used to compare if the mean values of two groups were significantly different. Meanwhile, a z-test was utilized to compare the proportion differences within categorical variables. A 2-tailed value of p < 0.05 was established as the threshold of statistical significance. All data analyses were performed using R language (ver 3.6.3).

# **Data Preprocessing**

In this study, records that were missing more than 50% of the feature values were considered noise data and deleted from the dataset. We also deleted records where more than 20% of the feature values were missing because there were too much missing data to all them. For the remaining missing values, we used multivariate imputation via the chained equations method.

The feature indices of the patients were of different dimensions or dimension units. This caused data with different attributes to be in different orders of magnitude. This might have, in turn, caused a few indicators to be ignored, which affected the results of the prediction model. After normalization

TABLE 1 Demographic and clinical data before normalization in tremor (Train_1) and non-tremor (Train_0) patients of the training data set.
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CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9000.238PTA114.8136.191112.5702.630PTA0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	Variable	Train_1_mean	Train_1_conf	Train_0_mean	Train_0_conf	p value
WBC         7.03         1.047         8.083         0.125           LYMPLpat         31.019         3.062         29.323         1.397           MNNDR,pdt         3.575         0.643         5.683         0.443           E0.pdt         2.306         0.762         2.644         0.075           BSSD_pdt         0.300         0.148         0.264         0.075           NEUT         2.244         0.342         4.303         0.0467           NONO         0.401         0.074         0.423         0.036           MCNO         0.401         0.074         0.423         0.036           MCNO         0.403         0.014         0.174         4.043         0.037           RCC         4.573         0.177         4.004         0.173         1.131           MCT         4.0681         1.7354         4.1369         1.131           MCT         4.0681         1.7354         4.1369         1.131           MCT         4.0681         1.737         4.0211         0.037           MCT         3.031         0.0359         3.0397         1.037           MCT         3.041         0.330         3.0397         1.0	Age (years)	42.531	3.999	44.617	2.327	0.441
MBC         7.03         1.047         8.083         0.265           LVMPH_pat         31.519         3.062         23.23         1.597           MONDFLpat         5.375         0.643         5.683         0.445           E0_pct         2.306         0.782         2.848         0.0475           BASD_pct         0.306         1.48         0.264         0.071           NELT         0.306         0.143         0.264         0.037           NENT         0.304         0.014         0.467           MONO         0.401         0.014         0.038         0.038           MCN         0.023         0.014         0.878         1.197           MCT         4.0381         1.774         4.1368         1.171           MCT         0.0381         1.077         4.036         1.171           MCT         0.0391         0.0391         0.037         1.371           MCT         0.0391         0.0391         0.037         1.371           MCT         0.0391         0.0391         0.0371         1.371           MCT         0.0391         0.0391         0.0371         0.0391           MCT         0.0391 </td <td>Weight</td> <td>66.953</td> <td>3.554</td> <td>70.589</td> <td>2.107</td> <td>0.138</td>	Weight	66.953	3.554	70.589	2.107	0.138
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EO         0.167         0.064         0.184         0.068           BASO         0.023         0.0144         0.876         1.687           HGB         132.805         10.397         139.642         4.037           HGC         4.579         0.177         4.806         0.477           HGC         40.861         1.754         41.595         1.131           MGV         58.569         2.086         9.0274         1.174           MGHC         30.231         0.807         33.7.844         4.730           MGHC         30.241         1.017         4.2.211         0.997           RDW_SD         4.2.431         1.017         4.2.211         0.997           PLT         26.594         2.386         0.012         0.337           PDW         13.519         0.814         12.590         0.331           PCT         0.271         0.026         0.253         0.012           ALT         2.3.031         4.3.69         1.359         0.138           PLCR         31.311         2.580         1.319         0.814           ALT         2.575         1.911         4.510           ALT         3.5156						0.303
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HöB12,80510,397138,6424.037HCT40,8411.75441,5861.131HCT40,8411.75441,5861.131MCV40,8592.06692,2741.3897MCHC30,2310.80732,7913.897MCHC30,2310.80732,7344,730MCHC30,0313.68933,7,3844,730MCHC30,2310.8011.35,710.457RDW,SD42,4311.01742,2110.937PLT26,59423,47522,2530.012PCT0.2710.0260.2530.012PCT0.2710.0260.2530.012PLCR31,3112.5803.0191.187ALT23,0314.78613,7921.808AST21,7552.2782.7851.901AST1.2590.2991.3590.136ALT1.2590.2991.3590.136ALT1.2590.2991.3690.136ALT1.2590.2991.3690.136ALT1.2590.2991.3690.136ALT1.2590.2991.3690.136ALT1.2590.2991.3690.136ALT1.2590.2611.5021.603ALT1.2590.2561.6441.502ALT1.2590.2561.7411.502ALT1.2611.7421.4530.665 </td <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.670</td>						0.670
RBC         4.579         0.177         4.806         0.477           HCT         40.981         1.754         41.8568         1.131           MCV         89.599         2.086         90.274         1.174           MCH         30.231         0.907         32.791         3.897           MCHC         337.094         3.899         337.384         4.730           RDW_CV         13.028         0.330         13.357         0.457           RDW_SD         42.431         1.017         4.3211         0.037           PLT         2.66.594         22.475         242.530         0.139           PCT         0.231         0.336         10.679         0.337           PLGT         3.131         2.580         30.109         1.167           ALT         23.031         4.766         19.792         1.806           ASTALT         1.259         0.299         1.355         1.692           AGGAT         35.166         19.855         46.940         9.451           ASTALT         1.259         0.292         1.806         1.922           AGGAT         35.166         19.855         46.940         9.9220						0.647
HCT40.9811.75441.5861.131MCV80.5692.08690.2741.174MCH30.2310.90732.7913.897MCHC337.0843.689337.3844.730RDW_SD42.4311.01743.2110.337PLT256.59423.47524.253011.809MFV10.6910.38610.8790.337PCT0.2710.0260.2530.012PLCT0.2710.0260.2530.012PLCT21.8752.2781.808AST21.8752.2781.901ALT23.0914.76819.7321.808AST21.8752.2781.901ALT23.0966.6397.40609.920PCT35.16619.85546.9401.4510ALB23.5342.19025.6611.397GLO24.2661.6942.56461.015ALB2.35342.19025.6611.397GLO24.2661.6942.86460.073TEIL7.0751.2415.7740.714CHE11879.20012.81911646.82688.600DBIL2.3810.3632.8360.336CHE11879.20112.8133.86.913.330CHE11879.20212.8311.3802.629CHE11879.2033.2333.66.911.387CHE11879.2042.83411.3303.66 <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.173</td>						0.173
MCV         89.599         2.086         90.274         1.174           MCH         332.094         3.889         337.384         4.730           MCHC         337.094         3.889         337.384         4.730           RDW_CV         13.028         0.330         13.357         0.457           RDW_SD         42.431         1.017         43.311         0.937           PLT         256.594         23.475         2.42.530         10.397           PDW         13.319         0.814         12.569         0.337           PDT         0.211         0.026         2.253         0.012           PLCR         31.331         2.580         30.109         1.167           ALT         2.1875         2.278         1.301         3.55           AST/ALT         1.259         0.299         1.359         0.361           ALT         2.4875         2.461         51515         1.562           ALT         1.259         0.289         1.4515         1.562           ALF         2.533         0.665         7.441         1.439           ALT         1.2527         7.70.56         4.982           ALF         2.5						0.666
MCH         30.231         0.907         32.791         3.897           MCHC         337.094         3.689         937.384         4.70           RDW_CV         13.028         0.330         13.357         0.457           RDW_SD         42.431         1.017         43.211         0.937           PLT         266.594         23.475         242.530         11.009           MFV         10.591         0.388         10.679         0.319           PCT         0.271         0.026         0.253         0.012           PLGR         31.331         2.580         30.109         1.167           ALT         23.031         4.766         19.792         1.806           AST         21.875         1.806         1.359         0.138           AST         21.875         1.806         1.397         1.567           AST         21.875         1.661         1.592         1.561           ALP         63.006         6.639         7.4060         9.800           CIA         4.7622         2.461         51.515         1.592           ALB         2.3534         2.5681         1.057         1.667           ALB </td <td></td> <td>40.981</td> <td></td> <td>41.586</td> <td>1.131</td> <td>0.642</td>		40.981		41.586	1.131	0.642
MCHC         337,094         3.689         337,384         4.730           DWU_CV         13.028         0.330         13.357         0.457           PLW_SD         42.431         1.017         43.211         0.967           PLT         266.594         23.475         242.530         11.809           MPV         0.319         0.337         0.337           PDW         13.319         0.814         12.599         0.319           PCT         0.271         0.026         0.263         0.012           PLCR         31.331         2.580         30.109         1.167           ALT         1.275         2.278         22.785         1.901           AST         2.1875         2.278         22.785         1.901           ALT         1.299         0.299         1.589         0.138           ALT         1.287         74.060         9.820           ALT         1.287         1.587         1.592           ALT         1.287         1.587         1.592           ALT         1.684         2.664         1.015           ALT         1.684         2.664         1.0167           ALGELO	MCV	89.569	2.086	90.274	1.174	0.607
RDW_CV         13.028         0.330         13.357         0.457           RDW_SD         42.431         1.017         43.211         0.987           PLT         266.594         23.475         242.530         11.809           MFV         10.591         0.388         10.679         0.337           PCT         0.271         0.026         0.253         0.012           PLCR         13.311         2.580         30.109         1.167           ALT         23.031         4.786         19.792         1.808           ASTALT         1.259         0.299         1.359         0.138           Y_GGT         35.156         19.855         46.940         9.820           TP         47.822         2.461         51.515         1.592           ALP         47.822         2.461         51.515         1.592           ALB         2.3534         2.190         2.5846         1.015           ALB         2.3634         2.190         2.5846         1.015           ALB         0.363         0.865         7.441         0.714           CHE         11879.250         1238.819         1.646.826         588.500	MCH		0.907	32.791	3.897	0.550
FDW_SD         42.41         1.017         42.211         0.987           PLT         256.594         23.475         242.630         11.809           MPV         10.591         0.398         10.879         0.337           PDW         13.319         0.814         12.599         0.319           PLCR         31.331         2.580         30.109         1.167           ALT         23.031         4.766         19.792         1.808           AST         21.875         2.278         2.785         1.901           ASTALT         1.259         0.299         1.369         0.168           PLGT         35.156         19.855         46.940         1.4510           ALP         63.906         6.639         7.4050         9.920           CGT         35.158         19.855         46.940         1.501           ALB         23.534         2.160         3.60         1.691           ALB         23.534         2.163         0.073           DBIL         2.381         0.383         2.836         0.074           DBIL         2.381         0.833         36.697         17.896           DBIL         3.6353	MCHC	337.094	3.689	337.384	4.730	0.956
PLT         266,594         23,75         242,800         11,809           MPV         10,591         0.396         10,879         0.337           PDW         10,319         0.814         12,599         0.339           PCT         0.271         0.026         0.283         0.012           PLCR         31,331         2,580         30,109         1.167           ALT         23,031         4,766         19,792         1,808           AST         21,875         2,278         1,901           AST         35,156         19,855         46,940         1,4.510           ALP         68,3906         6,639         74,060         9,820           TP         47,822         2,461         51,515         1,592           ALB         23,534         2,190         25,681         1,015           GLO         1,009         0,122         1,063         0,073           TBIL         2,351         0,383         2,866         7,441         1,499           CREA         6,3672         6,436         103,666         20,774           UHEX         1,879         1,389         3,80,967         17,896           DBL <td>RDW_CV</td> <td>13.028</td> <td>0.330</td> <td>13.357</td> <td>0.457</td> <td>0.516</td>	RDW_CV	13.028	0.330	13.357	0.457	0.516
PLT256.59422.475242.50011.809MFV10.5910.39810.8790.337PDW13.3190.81412.5990.319PCT0.2710.0260.2830.012PLCR31.3312.58030.1091.167ALT23.0314.78619.7921.808AST21.8752.27822.7851.901AST35.15619.85546.9401.4.510ALP66.39974.0609.920TP47.8222.46151.5151.592ALB23.5342.19025.6811.397GLO24.2661.69425.6411.015DBL2.35310.3832.8660.386DBL2.3810.3832.866688.500DBL2.3810.8657.4411.499CREA63.6726.436103.66620.774UHEA1.89212.841913.896.96717.896DBL2.3330.6552.8933.280CREA8.47412.52777.0564.962UHEA5.5330.0541.389.0671.367CREA8.47412.52777.0564.962CREA6.36726.639103.6662.691CREA6.3730.0552.8931.368CREA6.36721.2811.3620.703UHEA1.0541.389.06671.3673.290CREA6.3730.0552.893 <td>RDW_SD</td> <td>42.431</td> <td>1.017</td> <td>43.211</td> <td>0.937</td> <td>0.459</td>	RDW_SD	42.431	1.017	43.211	0.937	0.459
MPV10.5910.39810.8790.337PDW13.3190.81412.5990.319PCT0.2710.0260.2830.012P_LCR31.3312.50030.1091.167ALT22.0314.76619.7921.808AST21.8752.27822.7851.901AST/ALT1.2590.2991.3590.136CGT35.16619.85546.9404.510ALP63.9066.6997.40609.920ALF24.2661.69425.6461.015ALF2.35342.19025.6811.397GLO24.2661.6942.8080.073TBIL7.0751.6678.6101.057DBIL2.8110.3832.8360.366DBIL4.6751.2415.7740.714CHEA65.6726.436103.66620.774UFEA/CREA8.6726.436103.66620.774UFEA/CREA8.6726.436103.66620.774UFEA/CREA6.5531.2042.8390.366CGL105.4251.2841.38902.269CA1.4830.6552.8331.687CA2.0330.0552.8331.687CA2.0430.0552.8391.368CA1.1841.17211.3820.703UFEA/CREA2.5251.26076.6325.6407UFEA/CREA2.5251.261		256.594	23.475		11.809	0.315
PDW13.3190.81412.5990.319PCT0.2710.0260.2630.012PLCR31.3312.58030.1091.167ALT23.0314.78619.7921.808AST21.8752.2782.27851.901AST1.2590.2991.3590.136ALP63.9066.63974.0609.920TP4.78222.46151.5151.592ALB23.5342.19025.6811.015ALSQLO1.0090.1221.0630.073DBIL2.3810.3832.8360.386DBIL4.6751.2415.7740.714DFEA63.6726.46910.66620.774UREA5.5330.6657.4411.439CREA63.6726.43610.866620.774UREA5.5330.6657.4411.439CREA63.6726.43610.8933.230CREA63.6720.5145.3430.136Ka4.1050.1094.8131.350CA2.0330.6657.4411.439CREA63.6721.28810.64331.367CA2.8.341.3003.2303.230GLU5.760.5145.3430.136Ka4.1050.1094.8131.350Na1.40840.945138.9900.269CA2.6251.28610.0030.663 <td>MPV</td> <td></td> <td></td> <td></td> <td></td> <td>0.448</td>	MPV					0.448
PCT         0.271         0.026         0.233         0.012           P_LCR         31.331         2.580         30.109         1.167           AT         23.031         4.786         19.792         1.808           AST         21.875         2.278         22.785         1.901           ASTALT         1.259         0.299         1.359         0.136           ALP         63.906         6.639         74.060         9.920           TP         47.822         2.461         51.515         1.592           ALB         23.534         2.190         25.646         1.015           ALGO         1.009         0.122         1.063         0.073           TBIL         7.075         1.567         8.610         1.057           DBIL         2.381         0.383         2.836         0.386           DBIL         4.675         1.241         5.774         0.714           CHE         11879.250         1288.819         11648.826         2.879           UREA         6.3672         6.436         10.3666         20.774           UREA         6.3672         6.435         13.830         3.230           UREA						0.069
PLCR         31.31         2.680         30.109         1.167           ALT         23.031         4.766         19.792         1.808           AST         21.875         2.2785         2.2785         1.901           ASTALT         1.259         0.209         1.369         0.136           ASTALT         35.156         19.855         46.940         14.510           AP         63.906         6.639         74.060         9.920           TP         47.822         2.461         51.515         1.592           ALB         23.534         2.190         25.681         1.015           GLO         24.266         1.094         25.686         0.073           GLU         7.075         1.567         8.610         1.057           DBIL         2.381         0.383         2.836         0.386           DIBL         4.675         1.241         5.774         0.714           CHEA         63.672         6.436         103.666         20.774           UPEA/CREA         84.74         12.527         77.056         4.982           UA         331.350         35.333         36.9697         1.386						0.210
Â.T23.0314.78619.7921.808AST21.8752.2782.27851.901AST/ALT1.2590.2991.3590.136y_GGT35.15619.85546.94014.510ALP63.9066.63974.0609.920TP47.8222.46151.5151.592ALB23.5342.19025.6811.397GLO24.2661.6942.5.6461.015ALFGLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL4.6751.2415.7740.714CHE11879.2501238.8191146.826588.500UREA63.6726.436103.66620.774UREA84.7412.52777.0564.982UA331.35035.333386.9871.7.896Bicarbonate28.1381.2042.89193.230GL1.054251.298105.4431.350Na140.8340.945138.9802.629CI0.64251.298105.4431.637Ca2.0330.0652.8931.368P1.2610.0631.3470.180UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.703UPRO2.8440.2612.9060.703UPRO2.8440.2612.9060.703UPRO2.8440.261<						0.385
AST1.218752.2782.27851.901AST/ALT1.2590.2991.3690.136_CGGT35.15619.85546.94014.510ALP63.9066.63974.0609.920TP47.8222.46151.5151.592ALB2.3.5342.19025.6811.397GLO24.2661.69425.6460.067TBIL7.0751.5678.6101.067DBIL2.3810.3832.2360.386DBIL4.6751.2415.7740.714CHE11879.2501238.8191164.6826588.500UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA63.6726.436103.66620.774UREA0.5760.0194.8131.500Na1.40.8340.045138.9802.629CL1.5760.0330.6552.9931.368P1.2610.0330.6810.024AG1.1841.17211.3820.703UPRO2.8440.2612.9960.131UPRO<	_					0.152
AST/ALT1.2590.2991.3590.136 $\gamma_{C}GT$ 35.16619.85546.94014.510ALP63.9066.63974.0609.920TP47.8222.46151.5151.592ALB23.6342.19025.6811.397GLO2.4.2661.69425.6461.015ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.366DBIL4.6751.2415.7740.714CHEA1879.250128.81911646.82620.774UREA6.36726.436103.66620.774UREA331.35035.333366.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.1094.8131.350Na140.8340.9451.3470.163Ca2.0330.0552.8931.368P1.2610.0631.3470.180UPROC2.8440.2611.3470.180UPROC2.8440.26177.895100.002UPROC2.8440.26177.895100.002UPROC11.8131.25177.895100.002UPROC2.80251.26076.6326.6407UPROC2.80261.26076.6326.6407UPROC2.8040.2669.9900.236UPRO3.						0.671
Y_CGT35.15619.85546.94014.510ALP63.0066.63974.0609.920ALP47.8222.6151.5151.592ALB23.5342.19025.6811.397GLO24.2661.69425.6461.015ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBL2.3810.3832.8360.366DBL2.3810.4867.0740.714CHE11879.2501238.81911646.826588.500UREA63.6726.46610.866.862.774UREA5.5330.6657.4411.439CHEA63.6726.46610.866.982.813UREA/CREA88.47412.52777.0564.982UA331.35035.333368.98717.896Bicarbonate28.1381.0428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na1.408340.0631.3470.180Mg0.8430.0330.8610.024AG1.1841.1721.3820.703UPRO2.8440.2612.9060.131UPROH3.3111.2517.7895100.002UPROH2.60251.260766.62256.407UPROH2.8040.2869.9900.238UPROH3.331 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>0.541</td></t<>						0.541
AP63.9066.63974.0609.920TP47.8222.46151.5151.592ALB23.5342.19025.6811.397GLO24.2661.69425.6461.015ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.386IDBIL4.6751.2415.7740.714CHE11879.2501238.81911648.226588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.4741.252777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.550Na140.8340.945138.9802.629C105.4251.298105.4431.637Ca2.0330.6652.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2669.9900.238PT9.7250.2669.990						0.476
TP47.8222.46151.5151.592ALB23.5342.19025.6811.397GLO24.2661.69425.6461.015ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.386DBIL4.6751.2415.7740.714CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CHEA6.86726.43610.366620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.0981.83,9802.629CI105.4251.298105.4431.637Ca2.0330.0552.8931.360Na1.08430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2617.9990.238PT9.7250.2669.9900.238PTA11.48136.191112.5702.630PTA19.9140.0261.1450.434PTT3.50631.711<						
ALB23.5342.19025.6811.397GLO24.2661.69425.6461.015ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.386IDBIL4.6751.2415.7740.714CHE11879.250128.81911646.82620.774UREA5.5330.6657.4411.439CHEA63.6726.436103.66620.774UREA/CREA88.4741.252777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0652.9931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131UPRO2.8440.2669.9900.238PTA114.8136.191112.5702.630PTA19.9140.0261.1450.434APTT3.6631.71141.1908.109						0.355
GLO         24.266         1.694         25.646         1.015           ALB/GLO         1.009         0.122         1.063         0.073           DBL         7.075         1.567         8.610         1.057           DBL         2.381         0.383         2.836         0.386           IDBL         4.675         1.241         5.774         0.714           CHE         11879.250         1238.819         11646.826         588.500           UREA         5.533         0.665         7.441         1.439           CREA         63.672         6.436         103.666         20.774           UREA         33.350         3.533         366.987         1.896           Bicarbonate         28.138         1.204         28.919         3.230           GLU         5.576         0.514         5.433         1.350           Na         140.834         0.945         138.980         2.629           Cl         105.425         1.298         105.443         1.637           Ca         2.033         0.065         2.893         1.368           P         1.261         0.063         1.347         0.180						0.045*
ALB/GLO1.0090.1221.0630.073TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.386IDBIL4.6751.2415.7740.714CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.04428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298106.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0212.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.131UPRO2.8440.2612.9060.238PTA114.8136.191112.5702.630PTA9.940.2269.9900.238PTA114.8136.191112.5702.630PTR0.9080.0289						0.183
TBIL7.0751.5678.6101.057DBIL2.3810.3832.8360.386IDBIL4.6751.2415.7740.714CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UREA/CREA28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_NBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTA9.9140.0289.9250.022INR0.9040.0289.1450.434APTT35.0631.71141.1908.109						0.241
DBIL2.3810.3832.8360.386IDBL4.6751.2415.7740.714CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.350353.33386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.26177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.523
IDBIL4.6751.2415.7740.714CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH2.502512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.021INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.206
CHE11879.2501238.81911646.826588.500UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333368.9877.7896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.288105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131URECH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	DBIL	2.381	0.383	2.836	0.386	0.293
UREA5.5330.6657.4411.439CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_MBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTA114.8136.191112.5702.630PTA19.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	IDBIL	4.675	1.241	5.774	0.714	0.187
CREA63.6726.436103.66620.774UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTA0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	CHE	11879.250	1238.819	11646.826	588.500	0.741
UREA/CREA88.47412.52777.0564.982UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PTA114.8136.191112.5702.630PTA0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	UREA	5.533	0.665	7.441	1.439	0.229
UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	CREA	63.672	6.436	103.666	20.774	0.081
UA331.35035.333386.98717.896Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	UREA/CREA	88.474	12.527	77.056	4.982	0.064
Bicarbonate28.1381.20428.9193.230GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	UA	331.350			17.896	0.009**
GLU5.5760.5145.3430.136Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	Bicarbonate					0.826
Ka4.1050.1094.8131.350Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.217
Na140.8340.945138.9802.629Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.633
Cl105.4251.298105.4431.637Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.521
Ca2.0330.0552.8931.368P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.992
P1.2610.0631.3470.180Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.566
Mg0.8430.0330.8610.024AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						
AG11.1841.17211.3820.703UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.664
UPRO2.8440.2612.9060.131U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	-					0.516
U_RBCH25.02512.60766.63256.407U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.808
U_WBCH3.3311.25177.895100.002PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109						0.688
PT9.7250.2669.9900.238PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	_					0.502
PTA114.8136.191112.5702.630PTR0.9080.0280.9250.022INR0.9140.0261.1450.434APTT35.0631.71141.1908.109	_					0.497
PTR         0.908         0.028         0.925         0.022           INR         0.914         0.026         1.145         0.434           APTT         35.063         1.711         41.190         8.109	PT	9.725	0.266	9.990	0.238	0.322
INR         0.914         0.026         1.145         0.434           APTT         35.063         1.711         41.190         8.109	PTA	114.813	6.191	112.570	2.630	0.484
INR         0.914         0.026         1.145         0.434           APTT         35.063         1.711         41.190         8.109	PTR	0.908	0.028	0.925	0.022	0.491
APTT 35.063 1.711 41.190 8.109						0.628
						0.491
FIB 4.171 0.294 4.150 0.192	FIB		0.294			0.925

(Continued on following page)

TABLE 1   (Continued) Demographic and clinical data before normalization in tremor	(Train_1) and non-tremor (Train_0) patients of the training data set.
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Variable	Train_1_mean	Train_1_conf	Train_0_mean	Train_0_conf	p value
Π	14.359	0.435	14.083	0.274	0.382
D_Dimer	428.094	301.594	478.054	132.936	0.756
Sex	16	32	53	149	0.185

using the common min-max standardization, all attributes of the original data were normalized to a (0, 1) range.

#### **Prediction Model Development**

In this study, a prediction model based on machine learning was developed. The recursive feature elimination (RFE) method was used for feature selection, which was combined with a neural network (NN) to form the classifiers to build the prediction model.

The selected patients were randomly divided into two separate data sets: 70% of the patients from our database were assigned to the training dataset (the algorithm creation group) and the remaining 30% were reserved as the external validation set (validation group) to obtain unbiased estimates of accurate classification rates and variable importance.

RFE is a greedy algorithm used to find the optimal subset of features. It searched the complete set as a starting point, and the prediction accuracy after 10-fold cross-validation was used for the estimation principle. After ranking, the most related features ranked the highest, and the lowest ranking features were assigned negative values at the end of the iteration. In this study, the steps of the algorithm were as follows: ① initialize the feature set H; ② select the classifier NN; ③ calculate the weight of each feature,  $h_i$ , in H (the principle gives the accuracy of NN); ④ delete the minimum weight feature,  $h_i$ , and update H; ⑤ repeat steps 3 and 4 until H has only one feature left; and ⑥ perform feature importance ranking (Chang et al., 2019).

The RFE-NN method can export a list in the decreasing order of importance of the features. From this sorted list, we could obtain a set of feature subsets  $H1 \subset H2 \subset Hn$  (*n* indicates the number of features included in the list; in this study, n is 64).  $H_1$ was composed of the first feature,  $H_2$  consisted of the top two features in the list, and so on. Hn represented the complete feature set. For a large number of features, RFE with cross-validation (RFECV) could be used to reduce the computation. In the exhaustive method, the number of all the subsets was 2<sup>64</sup>-1; however, the number of subsets that RFECV needed to verify was only 64. The 10-fold cross-validation used in this study was suitable for datasets with fewer data. The samples in the dataset were randomly divided into 10 subsets of mutexes and similar size. During training, nine subsets were chosen, in turn, to form the training set, and the remaining one subset formed the test set. This method allowed the model to be trained and tested 10 times using different training and testing sets. Every test yielded an accurate rate, and we took the average of 10 test results as the final result to evaluate the accuracy of the algorithm. Essentially, RFECV could cross-validate different combinations of features. The sum of the decision coefficients was calculated, and the optimal feature combination was selected based on the importance of different features to the accurate rate.

The single hidden layer NN model that was used to predict tremors consisted of input, hidden, and output layers. The input layer consisted of all the values from the input, which was, in our study, the numerical representation of the seven features selected by RFE. In the hidden layer, every perceptron unit took input from the input layer, subsequently multiplied, and added it to the initially random values. This initial output was activated by the ReLU activation function. The third layer was the output layer, and it took all the perceptrons in the previous layer as inputs, multiplied, and added their outputs to the initially random values. It was then activated by a sigmoid function. This layer outputted a value between 0 and 1, which, in this test, represented the likelihood of a patient developing tremors. The 10-fold crossvalidation was also used to tune the prediction model using the number of neurons in the hidden layer as the tuning parameter. The prediction performance was assessed by the corresponding area under the curve (AUC) of the receiver operating curve (ROC) for this model. The equations for accuracy (ACC), sensitivity (SE), and specificity (SP) are as follows:

$$SE = \frac{TP}{TP + FN},$$
  

$$SP = \frac{TN}{TN + FP},$$
  

$$ACC = \frac{TP + TN}{TP + FP + TN + FN}.$$

# RESULTS

#### **Patient Characteristics**

A total of 252 patients (98 men and 154 women; mean age of approximately 45 years) were included in this study, of which 39 patients (15.5%) developed tremors and 64 variables, including demographic information and laboratory values, were collected for each patient; 181 patients (of which 32 developed tremors) in

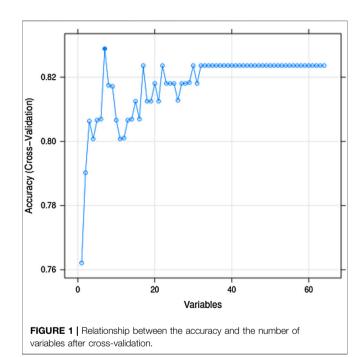
Variable	Accuracy	Accuracy SD	Kappa	Kappa SD	Selected
1	0.7621	0.041887	0.08312	0.24635	
2	0.7902	0.095455	0.06158	0.21474	
3	0.8063	0.099982	0.06627	0.24686	
4	0.8007	0.079142	0.04805	0.21157	
5	0.8066	0.084922	0.0463	0.19316	
6	0.8069	0.037175	0.05176	0.20010	
7	0.8288	0.137217	0.04763	0.28717	*
8	0.8174	0.036749	0.04558	0.20904	
9	0.8171	0.093225	0.03936	0.22117	
10	0.8066	-0.025062	0.03909	0.05452	
11	0.8007	-0.008761	0.04028	0.13650	
12	0.8010	-0.008866	0.04606	0.13657	
13	0.8066	-0.025062	0.03909	0.05452	
14	0.8069	-0.024476	0.03711	0.05369	
15	0.8125	-0.015385	0.03642	0.04865	
16	0.8069	-0.024476	0.03711	0.05369	
17	0.8236	0.030769	0.01823	0.09730	
18	0.8125	-0.015385	0.03642	0.04865	
19	0.8125	-0.015385	0.03642	0.04865	
20	0.8180	-0.009091	0.02282	0.02875	
21	0.8125	-0.015385	0.03642	0.04865	
22	0.8236	0.000000	0.01823	0.00000	
23	0.8180	-0.009091	0.02282	0.02875	
24	0.8180	-0.009091	0.02282	0.02875	
25	0.8180	-0.009091	0.02282	0.02875	
26	0.8128	-0.018286	0.03364	0.03855	
27	0.8180	-0.009091	0.02282	0.02875	
28	0.8180	-0.009091	0.02282	0.02875	
29	0.8183	009195	0.03176	0.02908	
30	0.8236	0.000000	0.01823	0.00000	
31	0.8180	-0.009091	0.02282	0.02875	
32	0.8236	0.000000	0.01823	0.00000	
33	0.8236	0.036364	0.03191	0.14969	
34	0.8236	0.000000	0.01823	0.00000	
35	0.8236	0.000000	0.01823	0.00000	
36	0.8236	0.000000	0.01823	0.00000	
37	0.8236	0.000000	0.01823	0.00000	
38	0.8236	0.000000	0.01823	0.00000	
39	0.8236	0.000000	0.01823	0.00000	
40	0.8236	0.000000	0.01823	0.00000	
41	0.8236	0.000000	0.01823	0.00000	
42	0.8236	0.000000	0.01823	0.00000	
43	0.8236	0.000000	0.01823	0.00000	
44	0.8236	0.000000	0.01823	0.00000	
45	0.8236	0.000000	0.01823	0.00000	
46	0.8236	0.000000	0.01823	0.00000	
47	0.8236	0.000000	0.01823	0.00000	
48	0.8236	0.000000	0.01823	0.00000	
49	0.8236	0.000000	0.01823	0.00000	
50	0.8236	0.000000	0.01823	0.00000	
51	0.8236	0.000000	0.01823	0.00000	
52	0.8236	0.000000	0.01823	0.00000	
53	0.8236	0.000000	0.01823	0.00000	
54	0.8236	0.000000	0.01823	0.00000	
55	0.8236	0.000000	0.01823	0.00000	
56	0.8236	0.000000	0.01823	0.00000	
57	0.8236	0.000000	0.01823	0.00000	
58	0.8236	0.000000	0.01823	0.00000	
59	0.8236	0.000000	0.01823	0.00000	
60	0.8236	0.000000	0.01823	0.00000	
61	0.8236	0.000000	0.01823	0.00000	
62	0.8236	0.000000	0.01823	0.00000	
	0.8236	0.000000	0.01823	0.00000	
63	0.0230	0.000000			

Note: The meaning of the bold values: when the number of variables was increased to seven, the accuracy was the highest.

our database were assigned to the training dataset; and the remaining 71 patients (of which seven developed tremors) were reserved as the external validation set. The clinical characteristics before normalization of the patients who developed tremors and those who did not in the training dataset before tacrolimus administration are shown in **Table 1**. There was no significant difference between the baseline values of most variables of the patients who developed tremors and those who did not, except for uric acid (UA) and total protein (TP) (p < 0.05).

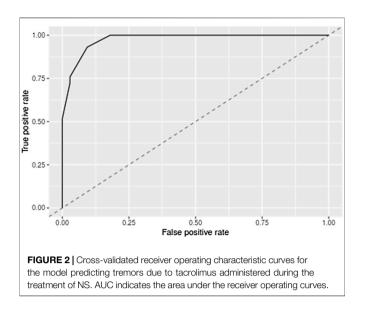
#### Variables of Importance

Generally, the error of a model decreases with an increase in the number of variables. However, increasing the number of variables is not suitable for clinical practice. To identify the prominent variables, we carried out feature selection using RFE. There were 64 variables in this study, and all



**TABLE 3** | Change in the AUC values when each variable is excluded from the model.

Variable	Value of AUC after excluding a variable	Change in the value of AUC after excluding a variable		
CREA	0.806	0.167		
D_Dimer	0.901	0.072		
TP	0.946	0.027		
Ca	0.874	0.099		
PDW	0.876	0.097		
Ka	0.884	0.089		
FIB	0.557	0.416		



combinations from 1 to 64 should be analyzed to select the subset of optimal features (highest accuracy). The outer resampling method: cross-validated (10-fold) could greatly reduce the computation. The results of the recursive feature selection on the training dataset are shown in Table 2. The accuracy values and kappa coefficients with standard deviations for each subset are also given in Table 2. A more intuitive diagram (Figure 1) shows the relationship between the accuracy and the number of variables after crossvalidation. When the number of variables was increased to seven, the highest accuracy was obtained (0.8288). When the number of variables gradually increased from 34 to 64, the accuracy remained constant. Therefore, the final model included seven indispensable features tremor for prediction: creatinine (CREA), D-dimer (D\_Dimer), total protein (TP), calcium ion (Ca), platelet distribution width (PDW), serum kalium (Ka), and fibrinogen (FIB). The top five variables (out of seven) were CREA, D\_Dimer, TP, Ca, and PDW. Moreover, the changes in the AUC values after excluding each variable were compared to re-evaluate the importance. The larger the change in the AUC value when a certain variable was excluded from the model, the more important the variable was assigned. The classification results were consistent, and there were only a few differences in the sorting of the importance of the variables. The changes in the AUC values when each of the seven variables was excluded from the model are shown in **Table 3**. Using this method based on the changes in the AUC values, the top five variables (out of seven) are FIB, CREA, Ca, PDW, and Ka. The former approach (**Table 2**; **Figure 1**) emphasized more on the importance of all of the variables as a whole to the model; however, the method based on the changes in the AUC values (**Table 3**) emphasized the impact of individual variables on the model. However, the aforementioned differences did not affect the classification results.

#### **Clinical Prediction Model**

After tuning the single hidden layer NN model, the optimal parameter was eight. This implied that when the number of neurons in the hidden layer was 8, the prediction model exhibited optimal performance. The model was then updated and retrained based on the tuning results. The ROC of the prediction model is shown in Figure 2, and the corresponding AUC value was 0.9726, which, being close to 1, implied that the classifier performed well. The AUC value was often used as an additional performance index. The accuracy, sensitivity, and specificity of the training set were 0.9345, 0.9712, and 0.7586, respectively. These results sufficiently indicated that a good distinction between the NS patients under tacrolimus therapy with and without tremors was obtained from this prediction model. To verify the performance of the developed model, we tested it based on a dataset containing seven patients with tremors and 64 patients without tremors as external validation. The comparison between the basic information of the training and validation sets is shown in Table 4. The external validation achieved an accuracy of 0.8214, a sensitivity of 0.8378, and a specificity of 0.7000. The accuracy, sensitivity, and specificity of the training and validation sets are shown in Table 5. These high prediction metrics indicate that the tuned prediction model could predict tremors effectively.

# DISCUSSION

NS is the most common clinical phenotype of immune-mediated glomerular diseases and is also the main cause of end-stage

Variable	Train_mean	Train_conf	Test_mean	Test_conf	p value
Sex	69	181	29	71	0.799
Age (years)	44.249	2.031	45.662	3.154	0.462
PDW	12.726	0.299	12.431	0.484	0.302
TP	50.862	1.388	50.041	2.479	0.548
CREA	96.595	17.247	91.982	13.514	0.752
Ka	4.688	1.110	4.038	0.102	0.471
Ca	2.741	1.125	2.327	0.546	0.656
FIB	4.154	0.165	4.119	0.275	0.824
D Dimer	469.221	120.527	378.014	101.869	0.375

TABLE 5	Prodiction	motrice	of the	training	and	validation	coto
TADLE 5	Frediction	metrics	or the	training	anu	valluation	Sets.

	Training set	Validation set
Accuracy	0.9345	0.8214
Sensitivity	0.9712	0.8378
Specificity	0.7586	0.7000

nephropathy (Gipson et al., 2016). Immunomodulatory agents, including glucocorticoids, are well-recognized therapeutic choices. In addition, calcineurin inhibitors (CNIs) suppress T cells and T-cell-dependent B-cell activation by blocking the phosphatase activity of calcineurin. CNIs such as tacrolimus are widely used for further immunosuppression in immune-mediated glomerular diseases, particularly in steroid-dependent and steroid-refractory NS (Floege et al., 2019). Although NS patients are treated with a smaller dose of tacrolimus than transplant patients, tremors are a major ADR of the nervous system that is often experienced by patients. Many patients with NS have to work and maintain a normal life, and the tremors that affected both the upper and lower limbs impacted the patients significantly.

In our study, the subjects clinically manifested NS. Even when the therapeutic dose of tacrolimus was maintained at less than 4 mg and the blood concentration was under 8 ng/ml, the occurrence of tremors was as high as 15.5%. The average age of patients was 42.5 years. Younger patients or those having greater demands at work may find it more difficult to deal with tremors. Unfortunately, there are few definitively effective strategies for prophylaxis or treatment of tremors caused by tacrolimus therapy. Therefore, it is necessary to establish a model that includes various factors related to patients that can prevent tremors, especially for those who might be at a higher risk of developing ADRs. One study also investigated the features (such as cholesterol plasmatic concentration) associated with the tremors caused by tacrolimus therapy; however, the results were also influenced by a single factor (cholesterol plasmatic concentrate), and further research needs to be conducted to evaluate the role of cholesterol plasmatic concentration in predicting the occurrence of tremors in patients under tacrolimus therapy (Erro et al., 2018). In this study, it was evident that seven variables (CREA, D\_Dimer, TP, Ca, PDW, Ka, and FIB) might have been related to the occurrence of predicted tremors, and we focused on the importance of all the variables as a whole on the occurrence of tremors, rather than individual variables. This is more consistent with the complex clinical reality. What is the theoretical relationship between these variables and the occurrence of tremors? CREA may affect the excretion of drugs including tacrolimus. Less excretion of drugs can lead to an accumulation of drugs in the body and increases the incidence of adverse reactions. Ca and Ka are ions that play an important role in the functioning and maintenance of muscle nerve conduction in the body. The change in the levels of Ca and Ka may also cause some kind of tremor. Therefore, it was not surprising that CREA, Ca, and Ka were associated with the occurrence of tremors. The remaining indicators seemed to correlate with the state of coagulation in the

body as a whole. It is worth noting that the clinical manifestations of NS patients are also hypoproteinemia and hypercoagulability. Therefore, we suspected that the occurrence of low-dose tacrolimus tremors is frequent, and the pathophysiological state of the NS (hypoproteinemia and high coagulation state) might have played a role. The effects of albumin and coagulation on drug entry into the body are mainly concentrated in drug distribution, especially for a high protein-binding drug (tacrolimus). Therefore, whether the special physiological state of tacrolimus affected its pharmacokinetic behavior remains to be studied. Meanwhile, further explanation of the influencing factors of tremors will depend on more experimental studies.

We have encountered many limitations in our study. A few basic characteristic variables might not have been included due to the lack of data such as blood lipids. Insufficient selection of categorical variables, drug interactions, and the use of a singlecenter study are a few other drawbacks of this study. The sample size of this study was small with a large number of variables, and this imbalance may have led to overfitting of the model, resulting in high accuracy. At the same time, the validation arm contains only a few patients with NS who developed tremors, and more patients are needed to be continued to better confirm the sensitivity and specificity of the algorithm. However, machine learning is a process that can be perfected by continuous training as new data are introduced. Anyway, this study offered one possible method for predicting tremors caused by tacrolimus in NS patients. The clinical application of this prediction model can identify the highrisk group of tremors early with a low dose of tacrolimus in patients with nephrotic syndrome and improve the treatment compliance of patients.

Many machine learning techniques have been widely used in medicine (Leung et al., 2013; Meng et al., 2019). RFE is popular machine learning technique because of its ease of configuration and use. RFE can be combined with different classifiers, such as NNs, support vector machines, and random forest (RF). Additionally, RFE is effective in selecting the features in a training set that are most relevant for variable prediction (Peng et al., 2019; Wottschel et al., 2019). In this study, a method combining RFE with RF was also developed to build a prediction model using the same data. RF was implemented by the RF function in R language (ver 3.6.3). It is an extension of the bagging method, which is a typical ensemble learning method. There are two main parameters in Rf: mtry (the number of variables randomly sampled as candidates at each split) and ntree (the number of trees to grow) (Rahman et al., 2017; Lai et al., 2020). In this model, every parameter of the optimal model can be tuned after the 10-fold cross-validation as follows: mtry was 9, ntree was 16, and nodesize (minimum size of terminal nodes) was 38. After calculation, the AUC value of the training set was 0.843, and the ACC value was 0.827. The external validation achieved an AUC value of 0.744 and an accuracy of 0.893. Evidently, the classification effect of the RF method was inferior to that of the NN. Notably, the number of tremors predicted by the RF method in the confusion matrix was 0. This implied that the RF method did not correctly predict tremors for the data used. The NN

## CONCLUSION

A risk prediction model with excellent predictive ability for tremors occurring during the treatment of NS patients using tacrolimus has been successfully established. This model can also be applied to patients who are administered with small doses of tacrolimus. It is the first model to include seven features: CREA, D\_Dimer, TP, Ca, PDW, FIB, and Ka. However, this study has encountered many limitations, including the exclusion of a few basic characteristic variables due to the lack of data on features such as the level of blood lipids, insufficient selection of categorical variables, drug interactions, and the use of a singlecenter study. The imbalance between the small sample size and a large number of variables may have led to overfitting of the model, resulting in high accuracy.

# DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

# ETHICS STATEMENT

The study protocol involving human participants were reviewed was approved by the Medical Ethical Committee of the Second Affiliated Hospital of Harbin Medical University (No. KY 2017-

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242). All subjects were anonymized, and the ethics committee approved waiving informed consent. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

### **AUTHOR CONTRIBUTIONS**

Du and Shao conceived of and designed the study. HZ, ZL, XH, and MM performed the data acquisition. ZD, BS, and YQ drafted the manuscript, conducted data analysis, and prepared the figures under the guidance of Xinyu Wang from the University of Virginia. Shao, Qu, and Zhang managed the patient data. All authors were involved in data interpretation and discussion of the results. The final version of the manuscript was approved by all authors.

#### FUNDING

This study were funded by the Young Scientist Fund of the National Natural Science Foundation of China (81903713) and the Natural Science Foundation of Heilongjiang Province (No. QC2018097).

#### ACKNOWLEDGMENTS

We would like to acknowledge Editage (www.editage.com) for English language editing.

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