


Development and Validation of a New Nomogram for Predicting Medication Nonadherence Risk in a Chinese Hyperlipidemia Population

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Purpose: This study aimed to explore the factors influencing medication adherence and develop a medication nonadherence risk nomogram in a Chinese population with hyperlipidemia.

Methods: This prospective intervention study was conducted in Beijing from November 2020 to October 2021. Medication adherence was determined according to the 9-question scale and nonadherence patients were intervened by pharmacists and followed up for 3 months. Multivariate logistic regression was used to analyze the risk factors of medication nonadherence, and then a nomogram model was established. The concordance index (C-index), area under the curve (AUC) was used to evaluate the accuracy of the prediction model. The decision curve analysis (DCA) and clinical impact plot analysis were employed to further evaluate the clinical effectiveness of the nomogram.

Results: A total of 685 patients were included for analysis. The rate of medication nonadherence was 238 patients (34.75%). Post-intervention, the average score of medication adherence increased from 20.75±8.01 to 29.90±6.93 ($p < 0.001$). And the number of patients with TC, TG, LDL-C, and HDL-C reaching the standard was 264 (62.86%), 201 (47.43%), 318 (78.52%), and 377 (96.71%), respectively. Five predictors including the course of hyperlipidemia (OR=2.957, 95% CI 1.168–7.488), following the doctor's advice to visit (OR=2.757, 95% CI 1.389–5.472), use of medications empirically (OR=1.189, 95% CI 1.188–2.786), physical exercise (OR=0.399, 95% CI 0.205–0.776) and lifestyle compliance (OR=0.910, 95% CI 0.839–0.988) were identified to build the nomogram model. The AUC was 0.927 and C-index was 0.87.

Conclusion: Patients with hyperlipidemia displayed low medication adherence which pharmaceutical interventions can improve. We developed and validated a nomogram model to facilitate the individual medication nonadherence risk prediction in hyperlipidemia patients.

Limitation: First, using the cut-off value of 27 for adherence assessment in the adherence questionnaire, criterion validity was not enough good to validly screen a patient with nonadherence to medication. Second, our study may have unmeasured confounding variables, which could bias the results. Third, owing to the lack of external validation in this study, it may have some limitations in extrapolation. Fourth, the questionnaire was assessed by self-report measures.

Keywords: hyperlipidemia, medication non adherence, risk factor, intervention, nomogram

Introduction

The high incidence of atherosclerotic cardiovascular and cerebrovascular diseases (ASCVD) endangers people's health and causes a major economic burden worldwide.^{1,2} Dyslipidemia is an independent risk factor for developing ASCVD.^{3,4} Thus, proper management in patients with dyslipidemia can reduce the incidence of cardiovascular and cerebrovascular

events. Currently, the primary strategies for managing hyperlipidemia encompass medication therapy and dietary intervention. Medication therapy is still the preferred strategy for improving hyperlipidemia, and statins are the first-line drug for the treatment of dyslipidemia.⁵ The effectiveness of treatment and prevention of ASCVD can be optimized with adherence to medication treatment. Previous studies have demonstrated that medication adherence has been playing quite an important role in the self-management of patients with hyperlipidemia.^{6,7} The good statin adherence can decrease the risks of all-cause and cardiovascular mortality.⁷ Medication nonadherence leads to poor control of blood lipids, which further develops into ASCVD. The annual direct and indirect cost of CVD and stroke in the United States is an estimated \$316.6 billion,⁸ and nonadherence is estimated to account for \$290 billion.⁹ At the same time, studies in China have found that patients with dyslipidemia in the community have poor adherence with statin medication.¹⁰ Medication nonadherence is affected by a variety of determinants,^{7,11} which can be summarized into socioeconomic factors (eg, social support, family income, medical expenses, nationality, and religious belief), patient-related factors (eg, age, sex, working condition, income, and education level), therapy-related factors (eg, drug usage and dosage, type and quantity of medicine, adverse drug reaction, side effects, and medication-related problems), and health system-related factors (eg, health providers, health status, medical insurance, drug supply). Results from previous studies have proved that pharmaceutical interventions could moderate the high risk of nonadherence and improve patients' long-term clinical outcomes.¹² Given so many associated risk factors, the development of accurate tools to predict nonadherence and early intervention may be the most effective strategy to ameliorate poor adherence. However, there are still few researches to explore medication nonadherence and its risk in patients with hyperlipidemia at present. In a US study, researchers evaluated multiple measures of patient previous medication adherence to predict future statin adherence by a large US administrative claims database. However, as the study required a longer retrospective period, this reduced the number of eligible patients, potentially limiting the generalizability of the prediction models. Meanwhile, there is a lack of prediction models of medication nonadherence in China.

As a commonly used clinical disease prediction tool, the nomogram refers to a two-dimensional chart illustrating the relationship between multiple risk factors, which is used to calculate the predictive probability of disease simply and efficiently.¹³ And the nomogram model has been widely used for clinical prediction of different diseases. The standard procedure for establishing nomogram model comprises: defining research objectives, determining outcome indicators, collecting population data, selecting appropriate models, selecting and finalizing contact real prediction variables and finally evaluating and validating the model.¹⁴

Therefore, this study aimed to investigate the current status of medication nonadherence and blood lipid control in patients with hyperlipidemia, identify potential risk factors of medication nonadherence, and develop a nomogram model to predict the risk of non-adherence. We also aimed to assess the effects of pharmaceutical interventions in improving patient adherence and blood lipid control through a pharmacist-led prospective study. The findings may provide evidence for more targeted interventions and further improve the therapeutic effect of medications in patients with hyperlipidemia.

Patients and Methods

Patients

This research was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (ethics number: KY2020-085-02). Written informed consent was obtained from each patient. This multicenter, prospective, interventional study was conducted in Beijing, China from November 2020 to October 2021. All data were collected from 35 hospitals that participated in the study. The inclusion criteria were as follows: (1) patients who were older than 35 years old; (2) patients who were diagnosed with hyperlipidemia by a doctor and received treatment with lipid-lowering drugs for at least 3 months; (3) patients with the ability to record medicine information, monitor blood lipid levels regularly, and follow-up for at least 3 months; and (4) patients that understand the questionnaire or scale after explanation and cooperate with pharmacists to complete the questionnaire. Patients who were suffered from a major mental disorder, illiterate, had severe cognitive impairment or had severe physical constraints were excluded. The collected data of the hyperlipidemia patients included 5 parts: (1) demographic and sociological characteristics of the patients (age, gender, marital status, income, occupational status, type of medical insurance, smoking history, alcohol

consumption history); (2) disease information (disease duration, history of the disease, complications, blood lipid monitoring results); (3) list of antihyperlipidemic drugs (types of drugs used, duration of medication, adverse drug reaction); (4) assessment of medication adherence (9-items Medication Adherence Assessment Scale, MAAS¹⁵); and (5) lifestyle compliance assessment. It refers to the degree to which individuals adhere to evidence-based health-related behaviors and medical recommendations in daily life, encompassing medication use, dietary management, physical activity, and regular health monitoring. It measured by self-report questionnaire (See [Supplementary Figure S1](#) for more details).¹⁵ There was a total of nine items with four options (score of 1–4). Here, the total is the sum of the scores for each question, with the highest score of 36. A higher score meant better compliance. Data such as demographic, blood lipid monitoring indicators such as low-density cholesterol, disease, and treatment characteristics of the patients were collected from medical records.

Medication Adherence Assessment

The Medication Adherence Assessment Scale (MAAS) was used to assess adherence in patients with hyperlipidemia. The MAAS consists of 9 items about taking medicine behavior in the past 3 months, in which patients were asked about the degree of agreement with statements. The nine items contained four forward questions and five reverse questions (see [Supplementary Figure S2](#) for more details). Answers are based on a 4-point Likert scale from 1 to 4 (1: Never; 2: Occasional; 3: Often; and 4: Always; or reverse scoring). The final score allows the identification of nonadherent patients, with 27 as the cut-off point, a higher score represents better adherence, and scores of 36, 27- < 36, and < 27 were defined as good, moderate, and poor adherence. In the multivariate logistic regression analysis, patients with moderate and good adherence were defined as the adherence group, while patients with poor adherence were defined as the non-adherence group. The study was conducted in the form of face-to-face interviews followed by interventions for non-adherence patients by specially trained pharmacists. Pharmacist-led interventions included recommendations on disease management, drug usage, and dosage, adverse effects, periodic monitoring indicators, medication reminders, strategies to improve medicine adherence, advice on lifestyle modifications, and so on. All patients were followed up three times, once a month. The first survey was defined as a baseline study. And the patients were scheduled for follow-up visits at one, two and three months. But the MAAS and serum concentrations of lipids was just surveyed at baseline and the third visit. At the first and second follow-up visits, only any medication related problems or adjustments were recorded. The screening flow chart of enrolled patients was listed in [Figure 1](#). Routine chemical methods were used to measure serum concentrations of lipids.

Statistical Analysis

Statistical analyses were performed using Microsoft Excel 2021 and IBM SPSS Statistics 26.0. The data were plotted using GraphPad Prism v5.0. Enumeration data were statistically described by frequency and rate (%), while the measurement data were expressed as the mean \pm SD. Descriptive statistics, chi-square (χ^2) test, and *t*-test were used to evaluate the results. Results were considered statistically significant if the *p*-value < 0.05. The nomogram model was developed using R software (version 4.2.2, <https://www.R-project.org>). Multivariate logistic regression analysis was conducted to screen potential risk factors for nonadherence in patients with hyperlipidemia, then a nomogram prediction model was established according to the corresponding risk factors, and the accuracy and clinical effect of the nomogram were verified. C-index and area under the curve (AUC) were selected to evaluate the differentiation ability of the nomogram.^{16,17} The nonadherence nomogram was verified by bootstrap validation (1,000 bootstrap resamples) to calculate a relatively corrected C-index.^{16,18} The decision curve analysis (DCA) and clinical impact plot analysis were employed to further evaluate the clinical effectiveness of the nomogram.

Results

Characteristics of Patients with Hyperlipidemia

There was a total of 685 patients included in the study. The average age was 63.95 \pm 11.08 years, including 297 males (43.36%) and 388 females (56.64%). The course of hyperlipidemia for more than 10 years was 199 (29.05%), and 526 (76.79%) patients

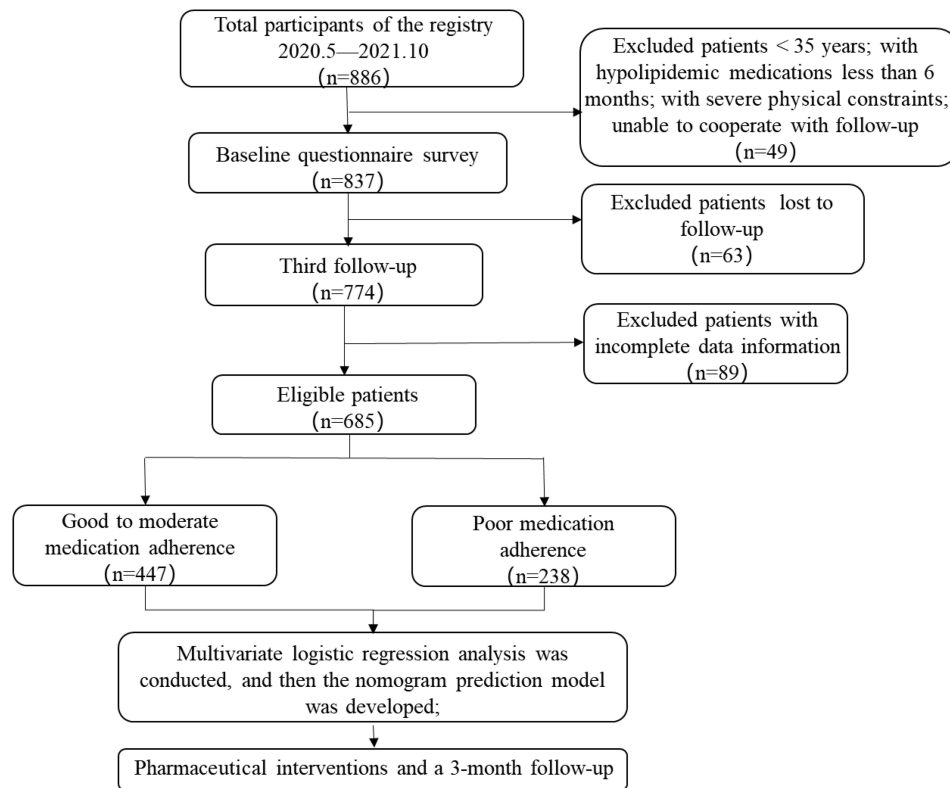


Figure 1 Screening flow chart of enrolled patients.

were taking statins for lipid-lowering treatment. According to the MAAS score, the hyperlipidemia patients were divided into 2 groups: the medication adherence (447 patients) and medication nonadherence (238 patients) groups. All characteristics of patients including demographic, disease, clinical characteristics, and treatment in the two groups were displayed in Table 1.

Table 1 Differences Between Demographic and Sociological Characteristics of Adherent and Nonadherent Hyperlipidemia Patients

Demographics	Grouping	No. of Patients, n (%)			Statistic	P-value
		Total (n=685)	Adherence (n=447)	Nonadherence (n=238)		
Sex	Male	297(43.36)	200(44.74)	97(40.76)	1.005	0.316
	Female	388(56.64)	247(55.26)	141(59.24)		
Age (years)	<45	38(5.55)	19(4.25)	19(7.98)	11.105	0.011
	45-70	463(67.59)	294(65.77)	169(71.01)		
	>70	184(26.86)	134(29.98)	50(21.01)		
Education level	Junior school	207(30.22)	133(29.75)	74(31.09)	0.983	0.612
	High school	334(48.76)	215(48.10)	119(50.00)		
	Undergraduate	144(21.02)	99(22.15)	45(18.91)		
^a BMI (kg/m ²)	<24	235(34.31)	156(34.90)	79(33.19)	0.661	0.718
	24~<28	309(45.11)	203(45.41)	106(44.54)		
	≥28	141(20.58)	88(19.69)	53(22.27)		
Smoking	Yes	108(15.77)	64(14.32)	44(18.49)	2.421	0.298
	No	577(84.23)	383(85.68)	194(81.51)		

(Continued)

Table 1 (Continued).

Demographics	Grouping	No. of Patients, n (%)			Statistic	P-value
		Total (n=685)	Adherence (n=447)	Nonadherence (n=238)		
Drinking	Yes	124(18.10)	84(18.79)	40(16.81)	0.700	0.705
	No	561(81.90)	363(81.21)	198(83.19)		
Marital status	Married	619(90.36)	405(90.60)	214(89.92)	2.791	0.425
	^b Other marital statuses	66(9.64)	42(9.40)	24(10.08)		
Working status	Be on the job	138(20.15)	81(18.12)	57(23.95)	3.929	0.140
	Retirement	503(73.43)	339(75.84)	164(68.91)		
	Others	44(6.42)	27(6.04)	17(7.14)		
Monthly per capita income (Yuan)	<5000	368(53.72)	231(51.68)	137(57.56)	4.114	0.391
	5000~10,000	253(36.93)	176(39.37)	77(32.35)		
	>10,000	64(9.34)	40(8.95)	24(10.08)		
Medical payment	Yes	560(81.75)	361(80.76)	199(83.61)	0.847	0.357
	No	125(18.25)	86(19.24)	39(16.39)		
Access to medical care	Convenient	642(93.72)	414(92.62)	226(94.96)	2.653	0.448
	Inconvenient	43(6.28)	33(7.38)	12(5.04)		
Course of hyperlipidemia (years)	≤1	68(9.93)	36(8.05)	32(13.45)	12.896	0.005
	2~5	248(36.20)	155(34.68)	93(39.08)		
	6~10	170(24.82)	108(24.16)	62(26.05)		
	>10	199(29.05)	148(33.11)	51(21.43)		
Combined chronic diseases	≤2	377(55.04)	234(52.35)	143(60.08)	6.806	0.078
	3	188(27.45)	123(27.52)	65(27.31)		
	≥4	106(15.47)	80(17.90)	26(10.92)		
Regular lipid monitoring	Yes	477(69.64)	300(67.11)	177(74.37)	3.867	0.049
	No	208(30.36)	147(32.89)	61(25.63)		
Received medication education	Yes	200(29.20)	138(30.87)	62(26.05)	1.747	0.186
	No	485(70.80)	309(69.13)	176(73.95)		
Knowledge of the lipid control level	Yes	206(30.07)	149(33.33)	57(23.95)	6.503	0.011
	No	479(69.93)	298(66.67)	181(76.05)		
Types of lipid-lowering drugs used	1	550(80.29)	352(78.75)	198(83.19)	3.168	0.205
	≥2	58(8.47)	41(9.17)	17(7.14)		
Take statins	Yes	527(76.93)	343(76.73)	184(77.31)	0.976	0.614
	No	158(23.07)	104(23.27)	54(22.69)		
Duration of lipid-lowering medication (year)	≤1	112(16.35)	62(13.87)	50(21.01)	15.014	0.005
	2~5	235(34.31)	142(31.77)	93(39.08)		
	6~10	119(17.37)	81(18.12)	38(15.97)		
	>10	134(19.56)	99(22.15)	35(14.71)		
Use of medications empirically	Yes	182(26.57)	87(19.46)	95(39.92)	33.481	<0.001
	No	503(73.43)	360(80.54)	143(60.08)		
Physical exercise	Always	136(19.85)	92(20.85)	44(18.49)	8.092	0.044
	Often	201(29.34)	139(31.10)	62(26.05)		
	Occasionally	225(32.85)	149(33.33)	76(31.93)		
	Never	123(17.96)	67(14.99)	56(23.53)		
Following the doctor's advice to visit	Never	41(5.99)	20(4.47)	21(8.82)	48.147	<0.001
	Occasionally	163(23.80)	74(16.55)	89(37.39)		
	Often	298(43.50)	214(47.87)	84(35.29)		
	Always	183(26.72)	139(31.10)	44(18.49)		
Lifestyle compliance (point)	>27	216(31.53)	164(36.69)	52(21.85)	36.798	<0.001
	18~27	414(60.44)	265(59.28)	149(62.61)		
	<18	55(8.03)	18(4.03)	37(15.55)		

Notes: ^aBMI= body mass index; ^bOther marital statuses: single, divorced, and widowed. Use of medications empirically: patients purchasing medicines by yourself based on your friends' recommendations, advertisements, or your own experience.

The Effect of Pharmacist Interventions on Medication Adherence

At the baseline, the patients with good, moderate, and poor compliance were 199 (29.05%), 248 (36.20%), and 238 (34.75%), respectively. Post-intervention, the patients with poor adherence was decreased significantly. And the patients with good, moderate, and poor compliance were 259 (37.81%), 244 (35.62%), and 182 (26.57%), respectively. A paired sample *t*-test was used to compare the correlation of medication adherence before and after the intervention. Post-intervention, the average score of medication adherence increased significantly ($p < 0.001$) from 20.75 ± 8.01 to 29.90 ± 6.93 (Figure 2).

The Effect of the Pharmaceutical Intervention on Blood Lipid Control

Pre-intervention, there were 213 cases with $TC < 5.2$ mmol/L, 146 cases with $TG < 1.7$ mmol/L, 290 cases with $LDL-C < 3.4$ mmol/L, and 366 cases with $HDL-C \geq 1.0$ mmol/L. The goal attainment rates of TC, TG, LDL-C, and HDL-C were 50.71%, 34.68%, 71.06%, and 93.36%, respectively. Post-intervention, the number of patients with TC, TG, LDL-C, and HDL-C reaching the standard was 264 (62.86%), 201 (47.43%), 318 (78.52%), and 377 (96.71%), respectively. Independent sample *t*-test was used to compare the changes in the results of blood lipid before and after the pharmaceutical intervention, with statistically significant differences in TC, TG, LDL-C, and HDL-C ($p < 0.001$) (Table 2).

Risk Factors Associated with Medication Nonadherence

Patients with good to moderate adherence were divided into one group (adherence), and patients with poor adherence were divided into another group (nonadherence), and one-way ANOVA was conducted to detect risk factors of medication nonadherence between the two groups (Table 1). Age, course of hyperlipidemia, regular lipid monitoring, knowledge of blood lipid control level, duration of lipid-lowering medication, taking drugs empirically, physical exercise, following the doctor's advice to visit, and lifestyle compliance were the significant risk factors according to univariate analysis ($p < 0.05$). To reduce the influence of confounding factors, the factors identified above were further analyzed by multivariate logistic regression, and the prediction accuracy of the model was 72.7% (Table 3).

As the results are shown in Table 3, the factors that have a significant influence on medication nonadherence mainly include the course of hyperlipidemia (OR 2.957; 95% CI 1.168–7.488; $P=0.022$), use of medications empirically (OR 1.819; 95% CI 1.188–2.786; $P=0.006$), physical exercise (occasionally exercise (OR 0.457; 95% CI 0.213–0.977; $P=0.044$); often exercise (OR 0.399; 95% CI 0.205–0.776; $P=0.007$); always exercise (OR 0.462; 95% CI 0.251–0.857; $P=0.014$)), following the doctor's advice to visit (OR 2.757; 95% CI 1.389–5.472; $P=0.004$), and lifestyle compliance (OR 0.910; 95% CI, 0.839–0.988; $P=0.025$).

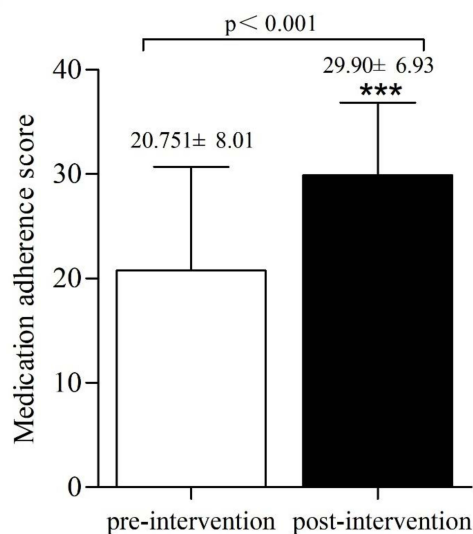


Figure 2 Comparison of changes in medication adherence pre- and post-intervention. ***: $P < 0.001$.

Table 2 The Effect of Blood Lipid Control Pre- and Post-Intervention

Items	Pre-Intervention [n (%)]	Post-Intervention [n (%)]	t	P value
TC (<5.2mmol/L)	213(50.71)	264(62.86)	9.767	<0.001
TG (<1.7mmol/L)	146(34.68)	201(47.43)	9.818	<0.001
LDL-C (<3.4mmol/L)	290(71.06)	318(78.52)	7.941	<0.001
LDL-C (<2.6mmol/L)	142(35.06)	204(50.37)		
HDL-C (\geq 1.0mmol/L)	366(93.36)	377(96.17)	8.120	<0.001

Notes: Independent sample t-tests were performed for changes in TC, TG, LDL-C, HDL-C before and after intervention.
Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3 Multivariate Logistic Regression Analysis of Risk Factors of Medication Nonadherence

Characteristic	OR ^a	95% CI ^b	p value ^c
Age group (set "<45" = 0)			
45~59	5.94	[0.832, 42.411]	0.076
60~70	2.37	[0.754, 7.445]	0.140
>70	1.826	[0.911, 3.66]	0.089
Course of hyperlipidemia, year (set " \leq 1" = 0)			
2~5	2.957	[1.168, 7.488]	0.022
6~10	1.495	[0.731, 3.06]	0.271
>10	1.619	[0.807, 3.247]	0.175
Duration of lipid-lowering medication, year (set " \leq 1" = 0)			
2~5	1.466	[0.698, 3.08]	0.313
6~10	1.895	[1.001, 3.587]	0.05
>10	1.53	[0.731, 3.201]	0.259
Regular lipid monitoring (set "Yes"=0)	1.475	[0.982,2.216]	0.061
Knowledge of blood lipid control level (set "Yes"=0)	0.734	[0.487,1.105]	0.139
Following the doctor's advice to visit (set "Yes"=0)	2.757	[1.389,5.472]	0.004
Use of medications empirically (set "No"=0)	1.819	[1.188, 2.786]	0.006
Physical exercise (set "never" = 0)			
Occasionally	0.457	[0.213,0.977]	0.044
Often	0.399	[0.205,0.776]	0.007
Always	0.462	[0.251,0.857]	0.014
Lifestyle compliance	0.910	[0.839,0.988]	0.025
Constant term	0.631		0.827

Notes: Use of medications empirically: patients purchasing medicines by yourself based on your friends' recommendations, advertisements, or your own experience. ^aOR, odds ratio. ^bCI, confidence interval. ^cp value by binomial logistic regression test, p = significance of different tests.

The course of hyperlipidemia, following the doctor's advice to visit, and use of medications empirically were positively correlated with nonadherence. Physical exercise and lifestyle compliance were negatively correlated with nonmedication adherence.

Risk Prediction of Nonadherence in Patients with Hyperlipidemia

We established a nomogram model for predicting nonadherence in patients with hyperlipidemia according to the above 5 risk factors (Figure 3). The AUC was 0.927, indicating favorable discrimination and accuracy by the medication nonadherence risk nomogram (Figure 4). The internal bootstrap resampling approach suggested the nomogram has sufficient discriminatory power with a C-index of 0.87. The calibration slopes of this study also exhibited good

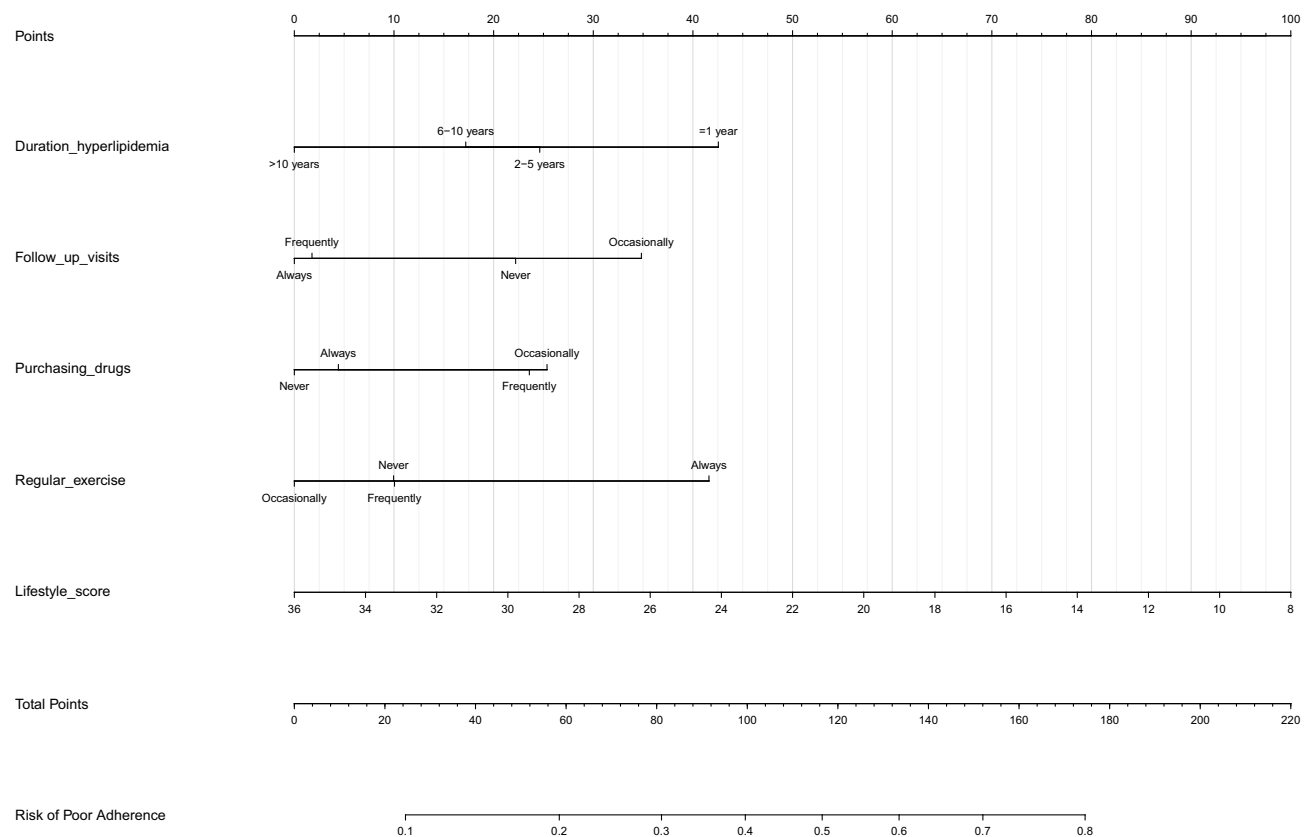


Figure 3 Nomogram prediction of medication nonadherence in patients with hyperlipidemia.

nomogram consistency, and the prediction ability was good (Figure 5). DCA (Figure 6) and clinical impact plot analysis (Figure 7) also demonstrated that the nomogram model performs well in clinical practice.

Discussion

The reported medication adherence of hyperlipidemia patients in our study was suboptimal but high compared to the global range.^{19,20} It was also higher than 57.9% from a previous study carried out in China.²¹ The findings indicated that the adherence of patients with hyperlipidemia had improved somewhat in recent years, although it was still not ideal. Previous studies have similarly found that medication nonadherence was higher for lipid-lowering medications among the four chronic disease medications assessed (including hypoglycemics, antihypertensives, lipid-lowering and antidepressants).²² Moreover, our study found that LDL-C control was better than 60.1% reported in a previous study in China²³ and 53.8% reported in a study in Spanish.²⁴ These results once again proved that improving adherence could ameliorate the control of hyperlipidemia. It was estimated that optimally controlled blood cholesterol would prevent 62% of coronary heart disease events.²⁵ The hyperlipidemia patients with ASCVD had higher LDL-C levels than patients without ASCVD,²⁶ indicating that more attention should be paid to medication adherence in hyperlipidemia patients with ASCVD.

Our results showed that 34.75% of patients with hyperlipidemia displayed medication nonadherence. Nonadherence negatively affects the efficacy, safety, and costs of therapies.²⁷ A variety of factors can contribute to nonadherence,¹⁹ which can be grouped into social and economic-related factors, therapy-related factors, patient-related factors, and health provider and health system-related factors.^{7,28} In the analysis of risk factors for medication nonadherence, we found that duration of hyperlipidemia, taking drugs empirically, physical exercise, following the doctor's advice to visit regularly, and lifestyle compliance were closely related to medication adherence. Patients with the duration of hyperlipidemia between 2 and 5 years were almost 3 times more nonadherent than patients with duration less than or equal to 1 year. The

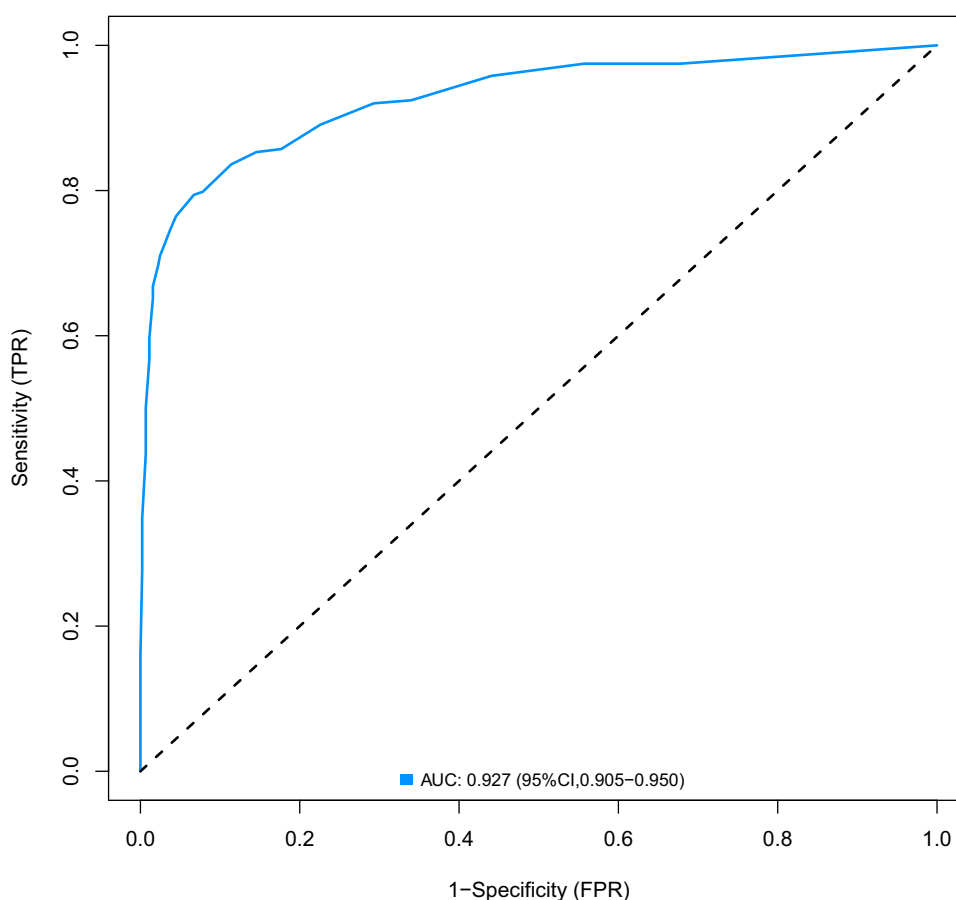


Figure 4 ROC curve based on the predictive nomogram for medication nonadherence in patients with hyperlipidemia. The dashed black line represents random performance (AUC=0.5), and solid blue line represents real performance (AUC=0.927).

risk of nonadherence in patients who did not follow the doctor's advice to visit were nearly 3 times that of patients who followed up periodically. Patients who take drugs empirically, who never exercise, or who were lifestyle noncompliant were more prone to nonadherence. Per a 1-point increase in lifestyle compliance score, the risk of nonadherence decreased by 9%.

Having effective, economical, and applicable techniques is essential for hyperlipidemia patients to change their adherence and improve their health. Pharmaceutical interventions constitute the primary strategies used to improve patient adherence.²⁹ The findings of our study provided scientific evidence of the effectiveness of pharmaceutical interventions to improve the blood lipid control in patients with hyperlipidemia and reduce the number of patients with medication non-adherence, consistent with the previous study in which among participants taking lipid-lowering medication, low adherence was associated with higher mean LDL-C.³⁰ Pharmaceutical interventions in our study involved comprehensive interventions and frequent contact with patients, which prompted that multi-faceted interventions were more likely to be effective in improving the overall outcome measures. Our results underscore the need for multidimensional interventions aimed at improving medication adherence and the overall health of patients with hyperlipidemia according to adherence risk factors. With the development of the Internet and the popularization of telemedicine, Telematics interventions can be used to improve patients' medication adherence and clinical outcomes. A systematic review confirmed that telehealth modalities including eHealth and telehealth medication adherence interventions were associated with improved adherence.³¹ Future research could incorporate telehealth modalities interventions into multi-faceted measures to improve effectiveness.

However, nonadherence is a multifactorial problem, factors influencing medication adherence vary across studies.^{32,33} An overview of systematic reviews suggested that there was a social gradient in adherence. Whereas, for most factors,

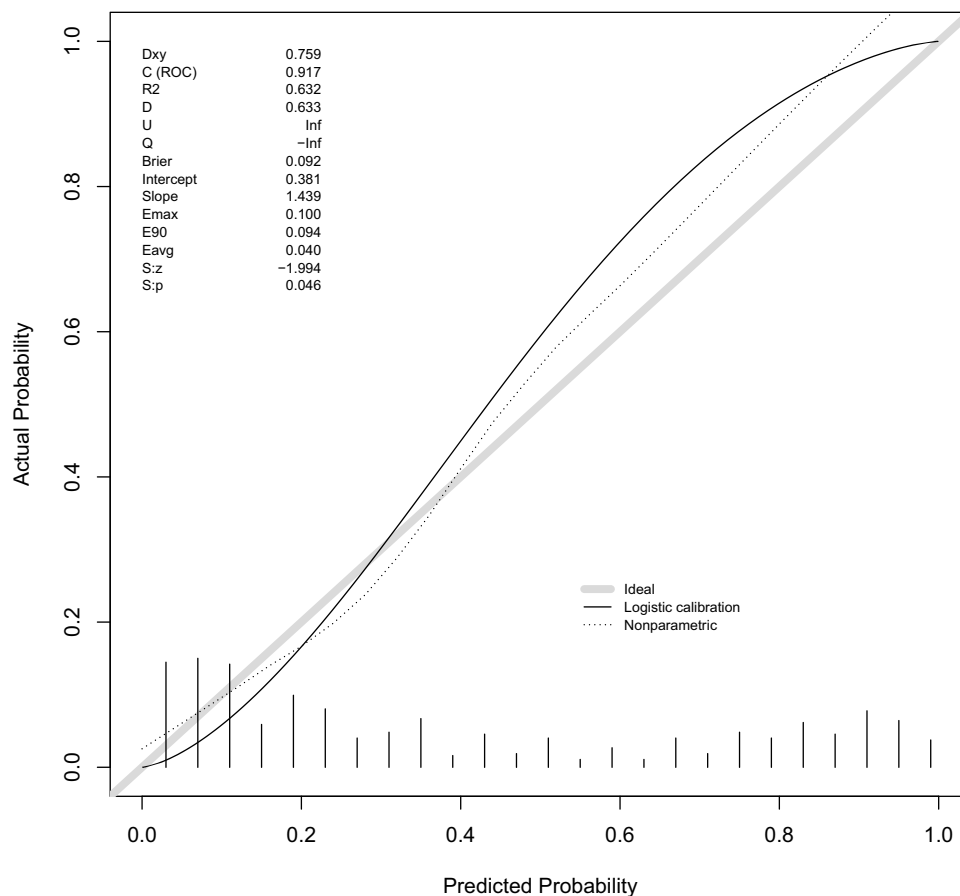


Figure 5 Calibration slopes of the nonadherence nomogram prediction.

the evidence was not conclusive due to the risk of bias, inconsistency, or imprecision.²⁷ In clinical practice, interventions could focus on the risk factors to improve antihyperlipidemic medication adherence. The nomogram model is a simple and effective tool to identify patients with high risk of nonadherence and can provide evidence for more targeted interventions. Nomograms have been widely used in the field of diagnosis and prognosis of diseases, such as oncology,^{34,35} hypertension,³⁶ and in recent years have been successfully used in the prediction of medication nonadherence.^{17,18,37} To the best of our knowledge, this is the first study to use a nomogram to predict medication nonadherence in hyperlipidemia patients. The nomogram was established based on the five risk factors of a multivariate Logistic regression analysis of medication adherence. The internal bootstrap resampling approach suggested the nomogram has sufficient discriminatory power with a C-index of 0.87. The calibration slopes also showed good consistency between the prediction and the observation. In recent years, many models for predicting disease risk factors have been mentioned in a few studies,^{38–40} but few for non-adherence.⁴¹ Compared to individual risk factors, the predictive model based on several risk factors is further capable of assisting the clinician in noticing the patients who are prone to non-adherence. Therefore, we presented and validated a nomogram, which is constructed by non-adherence influencing variables. Clinicians can utilize this model to estimate the risk of nonadherence and make preventions accordingly.

This study exhibits several notable strengths. First, it adopts a multicenter, prospective interventional design conducted across 35 hospitals in Beijing, ensuring a large and representative sample of 685 hyperlipidemia patients, which enhances the generalizability of findings within the population of Beijing districts. Second, the study integrates pharmacist-led comprehensive interventions, demonstrating significant improvements in both medication adherence and blood lipid control, providing direct evidence for clinical practice. Third, it identifies five key predictors of medication nonadherence through multivariate

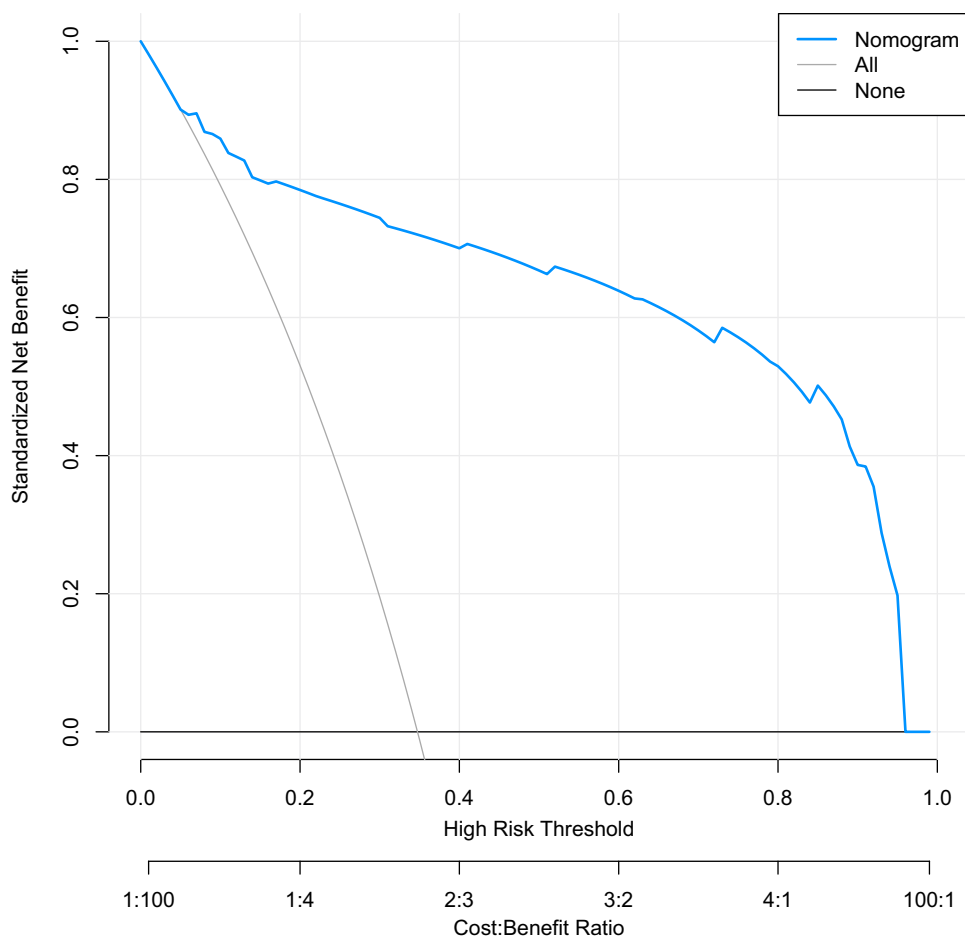


Figure 6 DCA of the nonadherence nomogram prediction.

logistic regression, constructing a nomogram model with acceptable discriminative ability and good calibration. It is an individualized assessment tool for predicting risks of medication non-adherence, rarely reported in hyperlipidemia research.

This study has some limitations. First, using the cut-off value of 27 for adherence assessment in the adherence questionnaire, criterion validity was not enough good to validly screen a patient with nonadherence to medication. This may bias the determination of nonadherence. Second, our study may have unmeasured confounding variables, which could bias the results. For example, we did not investigate information about socioeconomic factors⁴² and health literacy,⁴³ which were found to be important barriers to medication adherence. Third, although the robustness of our nomogram has been validated internally, we did not verify the nomogram externally. Therefore, it cannot be applied to hyperlipidemia populations in other regions and countries. It needs to be externally evaluated in a wider population with hyperlipidemia. Fourth, the questionnaire was assessed by self-report measures, which may be subjected to self-report biases.

Conclusion

(1) This study revealed a high rate of nonadherence to medication treatment for hyperlipidemia but it may possible to improve it by pharmacist-led interventions. Therefore, pharmacist-led interventions should be encouraged in the management of hyperlipidemia patients. (2) Medication nonadherence was significantly associated with long duration of hyperlipidemia, taking drugs empirically, never physical exercise, not following the doctor's advice to visit regularly, and poor lifestyle compliance. And we developed a nomogram model with a relatively accurate predictive ability by internal validation. In future, we hope to integrate this model with community health records, thereby helping doctors identify high-risk hyperlipidemia patients with poor medication adherence.

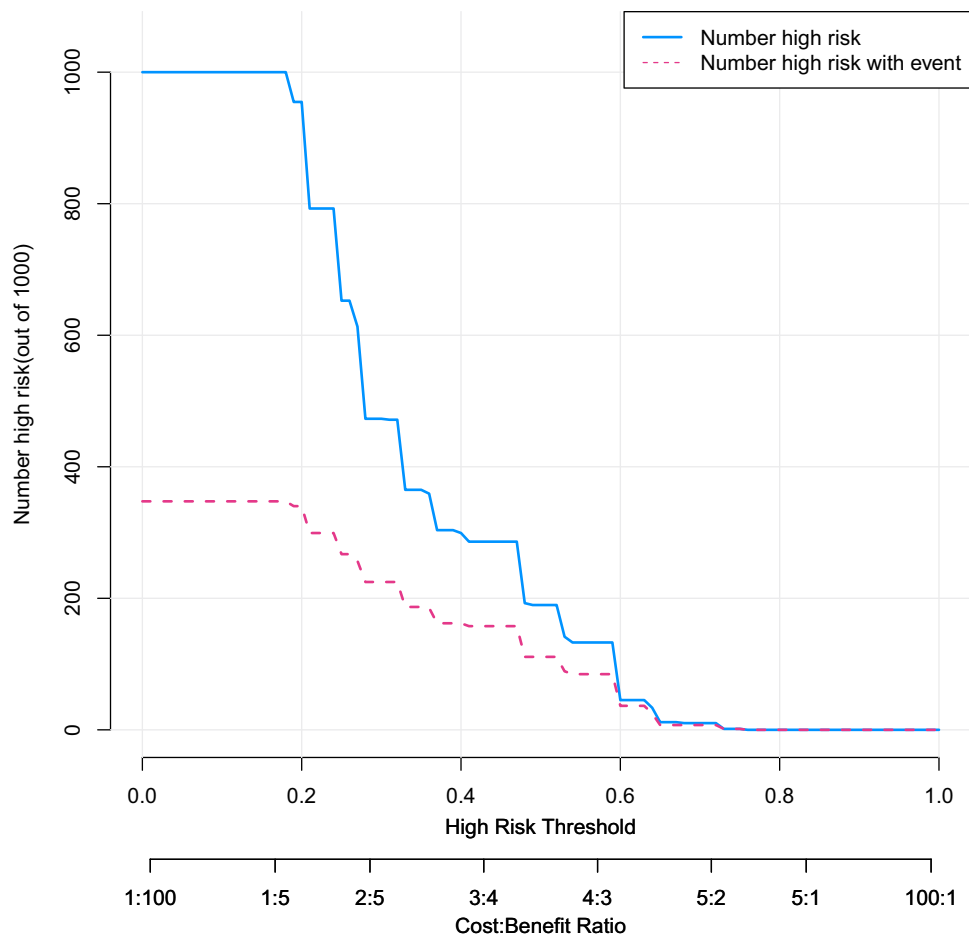


Figure 7 Clinical impact plot analysis of the nonadherence nomogram prediction.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The research was following the Declaration of Helsinki. The study was approved by the Ethics Committee of Beijing Tiantan Hospital, the reference number KY2020-085-02. Informed written consent has been obtained from each patient after a full explanation of the purpose and nature of all procedures used.

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Disclosure

The authors report no conflicts of interest in this work.

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