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Original Article

Development of a nomogram to predict medication nonadherence risk in patients with rheumatoid arthritis

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Abstract: Objectives: Poor adherence among patients with chronic diseases including inflammatory rheumatic diseases (IRDs) is a complex and serious global health care problem. This study aimed to develop an intelligent nomogram using retrospectively collected patient clinical data for predicting nonadherence to biologic treatment in rheumatoid arthritis (RA) patients. Methods: The clinical characteristics of 102 RA patients were collected from outpatients and inpatients at the Orthopedic Departments of Ningxia General Hospital of Ningxia Medical University and Ningxia Hui Autonomous Region People's Hospital from October 2020 to September 2021. Adherence was evaluated using the proportion of treatment days covered within 6 months as the outcome event. A least absolute shrinkage and selection operator (LASSO) regression analysis was used to identify risk predictors, and then multivariate logistic regression analysis was applied to construct the risk prediction model. Furthermore, the nomogram was plotted by multivariable logistic regression. Results: Among the 102 patients analyzed, 43 patients did not adhere to biologic therapy for various reasons. LASSO regression analysis identified age, sex, education level, disease activity, monthly income, medical insurance, and adverse drug reactions as the significant risk predictors. By incorporating these factors, the nomogram was plotted which showed good discrimination, calibration, and clinical value. The C-index was 0.759 (95% CI: 0.665-0.853), and the area under the receiver operating characteristic (ROC) curve was 0.7416 with a good calibration ability. Decision curve analysis showed that the prediction effect of this model could benefit about 75% of the patients without compromising the interests of other patients. Conclusions: This nomogram could help medical staff identify patients with higher risk of nonadherence early, so that intervention measures can be taken in time.

Keywords: Rheumatoid arthritis, chronic diseases, nonadherence, nomogram, R software

Introduction

Nonadherence, defined as the extent to which a patient's behavior does not correspond to the agreed prescription, is a common problem and has a significant impact on the treatment efficacy and the healthcare cost in patients with chronic diseases such as RA [1]. RA is a common autoimmune disease characterized by chronic inflammation and joint swelling. The onset of RA is between the ages of 20 to 50, and the incidence of RA in females is two to three times higher than that in males [2]. The main pathological symptom of RA is chronic inflammation of the synovial membrane, which causes joint destruction and limited function, leading to poor quality of life of patients [3-5].

The importance of patient involvement in decision making underscores the need to examine the concept of adherence in chronic disease. In RA, nonadherence can lead to treatment failure, delayed recovery, accelerated disease progression, and more aggressive treatment. In addition, patients with RA often have related comorbidities and therefore are often treated with multiple medications, which further worsens the medication adherence [6].

Moreover, there are other determinants that affect medication nonadherence, including socioeconomic factors, e.g., practical social support, emotional support, marital status, and family cohesiveness [7], condition-related factors, e.g., health condition, work intensity, and medical insurance, and therapy-related factors, e.g., medicine dose, type of medicine, amount of medicine, side effects, and medicine-related questions. The patient's personal information such as age, sex, employment, education level, income, degree of education, and distance to the hospital also influences the medication nonadherence [8, 9]. With so many risk variables involved, the development of methods for early intervention and accurate prediction of adherence may help circumvent the adherence issue. Understanding the risk factors underlying nonadherence is critical in designing effective intervention strategies. Given the existence of a large number of relevant factors affecting medication nonadherence, it is significant to establish an accurate adherence prediction tool for the early intervention and the improvement of nonadherence [10]. Therefore, the aim of this study was to construct a nonadherence risk predicting model that could help provide a comprehensive and effective treatment for RA patients.

Methods

Study population and ethical approval

This retrospective study collected the clinical information of 102 RA patients who were treated as inpatients and outpatients in the Orthopedic Departments of Ningxia General Hospital of Ningxia Medical University and Ningxia Hui Autonomous Region People's Hospital from October 2020 to September 2021. All patients were first-time users of biologics including etanercept (58) and adalimumab (44).

The patient's inclusion criteria were: 1) met the disease diagnostic criteria in the American College of Rheumatology in 1987; 2) provided informed consent to participate; and 3) had basic literacy skills and were able to communicate effectively.

The exclusion criteria were: 1) patents with severe mental disorders and dementia; 2) those with combined malignancies; 3) patients who had severe ongoing infections; 4) those who were hypersensitive to the active substance or any of the excipients; and 5) anyone who was pregnant [11, 12]; 6) anyone with incomplete patient information or medical records.

This study was performed in accordance with the ethical principles as stated in the Declaration of Helsinki and approved by the Medicine Ethics Committee of Ningxia Medical University (Approval No.: 2020-974). All patients were informed about the purpose and methods of the study and signed the informed consent form. All participants provided written informed consent, filled out questionnaires evaluating treatment adherence. This study de-identified all patient data.

Adherence assessment

All patients were interviewed by nurses for 20 min before the first use of biologics, and the patient information including age, disease activity of 28 joints (DAS28), gender, education level, distance from residence to hospital, monthly income, health insurance coverage, work intensity, treatment convenience, adverse drug reactions, and doctor-patient trust was collected. Hamilton Anxiety Scale was used to assess patients' anxiety [13], while the convenience of drug use was assessed according to whether it was pre-filled or non-pre-filled. Doctor-patient trust was measured using the revised version of the Wake Forest Physician Trust Scale [14], with strong agreement and comparative agreement as the indicators of patient trust. To determine the adverse drug reactions, the patients were followed up within 1 week after the first treatment, followed by outpatient follow-up at 1, 2, 4, and 6 months. The following symptoms were considered adverse reactions: the occurrence of injection site allergy, abnormal liver and kidney function, skin and subcutaneous tissue abnormalities at the injection site, hematologic effects, and recurrent infections. Data on 12 categories were collected for predictor screening in this study.

The proportion of days covered (PDC) is one of the criteria to measure adherence to drug therapy and has been proposed by the National Quality Forum to be used as an indicator to assess drug adherence [15, 16]. PDC is the

Table 1. Factors conversion

Factors	0	1	2	3
Age/years	< 50	≥ 50		
Sex	Male	Female		
Education level	junior high school and below	high school	college and above	
Distance to hospital/km	< 20	≥ 20		
Disease activity		DAS28 score < 5.1	DAS28 score ≥ 5.1	
Monthly income	< 5,000	5,000-10,000	> 10,000	
Medical insurance	Yes	No		
Work intensity	Less activities	Light to moderate activity	Medium and above activities	
Convenience of medication use	Yes	No		
Adverse drug reactions	Yes	No		
Anxiety level	Never	Mild	Moderate	Severe
Doctor-patient trust	Yes	No		

ratio of time covered by drug application to the total time applied with PDC > 80% being considered good adherence [14]. The starting point of the follow-up in this study was the initiation of biologic agents by patients, and all patients were followed up in outpatient clinics at 1-, 2-, 4-, and 6-months post treatment. The endpoint was whether they continued to use biologic agents at the last follow-up visit of 6 months, along with the hospital e-prescribing system, to finally arrive at the PDC.

Nomogram construction

A nomogram was constructed by generating risk scores for each patient based on a linear combination of selected features and the corresponding weighted coefficients from the LASSO analysis. These factors were used to generate a multivariable logistic regression model and a corresponding nomogram.

Statistical analysis

Statistical analysis and R package rms plotting nomogram were performed using R software (version 4.1.2; https://www. R-project.org). All data, including number of patients and disease characteristics, were expressed as percentages (%). The chi-square test was used to analyze qualitative variables. Values of $P < 0.05$ were considered statistically significant. LASSO regression analysis was used to screen the significant factor among the 12 factors. The factors were converted during data entry in R software as shown in **Table 1**. Based on the factors screened by LASSO regression, multivariate logistic regression analysis was used to build the prediction model and plot the nomogram. The accuracy of the prediction model was assessed by plotting calibration curves. Harrell's C-index was calculated to determine the discrimination ability of this nonadherence nomogram. To further determine a substantially adjusted C-index, the nonadherence nomogram was performed with bootstrapping validation (1,000 bootstrap resamples). Moreover, area under the ROC curve values were computed to gauge nomogram discrimination capabilities. The net benefit was calculated by subtracting the proportion of all patients who were false positives from the proportion of the patients who were true positives and by weighing the relative distress of forgoing interventions compared with the negative consequences of an unnecessary intervention.

Results

Patient characteristics

In this study, a total of 102 patients (20 males and 82 females) were included with a mean age of 42.47±9.32. Among the 102 cases, 59 (57.84%) cases belonged to the adherence group, while the other 43 cases were in the nonadherence group. Between the adherence and the nonadherence groups, there were statistically significant differences in sex ($P = 0.001$), education level ($P < 0.0001$), disease activity ($P = 0.006$), and anxiety level ($P < 0.0001$). However, there were no significant differences in other characteristics between the

Table 2. Clinical characteristics of patients

Demographic characteristics	Adherence/ [n (%)]	Nonadherence/ [n (%)]	Total/ [n (%)]	χ^2	*P* value
Age/years					
< 50	25 (42.4)	17 (39.5)	42 (41.2)		
≥ 50	34 (57.6)	26 (60.5)	60 (58.8)	0.083	0.774
Sex					
Male	26 (44.1)	19 (44.2)	45 (44.1)		
Female	33 (55.9)	24 (55.8)	57 (55.9)	0.000	0.991
Education level					
junior high school and below	7 (11.9)	11 (25.6)	18 (17.6)		
high school	5 (8.5)	15 (34.9)	20 (19.6)		
college and above	47 (79.6)	17 (39.5)	64 (62.8)	59.732	< 0.0001
Distance to hospital/km					
< 20	45 (76.3)	30 (69.8)	75 (73.5)		
≥ 20	14 (23.7)	13 (30.2)	27 (26.5)	0.541	0.462
Disease activity					
DAS28 score < 5.1	34 (57.6)	32 (74.4)	66 (64.7)		
DAS28 score ≥ 5.1	25 (42.4)	11 (25.6)	36 (35.3)	3.071	0.096
Monthly income/yuan					
< 5,000	11 (18.6)	9 (20.9)	20 (19.6)		
5,000~10,000	28 (47.5)	14 (32.6)	42 (41.2)		
< 10,000	20 (33.9)	20 (46.5)	40 (39.2)	2.416	0.299
Medical insurance					
Yes	37 (62.7)	26 (60.5)	63 (61.8)		
No	22 (37.3)	17 (39.5)	39 (38.2)	0.053	0.818
Work intensity					
Less activities (clerks, etc.)	16 (27.1)	12 (27.9)	28 (27.5)		
Light to moderate activity (renovators, etc.)	26 (44.1)	18 (41.9)	44 (43.1)		
Medium and above activities (agriculture and animal husbandry, etc.)	17 (28.8)	13 (30.2)	30 (29.4)	0.051	0.975
Convenience of medication use					
No	32 (54.2)	28 (65.1)	60 (58.8)		
Yes	27 (45.8)	15 (34.9)	42 (41.2)	1.215	0.270
Adverse drug reactions					
No	33 (55.9)	22 (51.2)	55 (53.9)		
Yes	26 (44.1)	21 (48.8)	47 (46.1)	0.228	0.633
Anxiety level					
Never	24 (40.7)	10 (23.3)	34 (33.3)		
Mild	26 (44.1)	12 (27.9)	38 (37.3)		
Moderate	6 (10.2)	15 (34.9)	21 (20.6)		
Severe	3 (5.0)	6 (13.9)	9 (8.8)	13.605	0.003
Doctor-patient trust					
No	33 (55.9)	25 (58.1)	58 (56.9)		
Yes	26 (44.1)	18 (41.9)	44 (43.1)	0.049	0.824

adherence and the nonadherence groups. The detailed results were shown in **Table 2**.

LASSO regression analysis

We further identified seven factors: Age, sex, education level, disease activity, monthly income, medical insurance status, and adverse drug reactions as the predictors of patients' nonadherence to biologics (**Figure 1**). These seven factors were included in the multivariate logistic regression analysis, and the results filtered out five of them which were used in the prediction model to construct the nomogram. These 5 factors were age, disease activity, monthly income, medical insurance status, and adverse drug reactions (β = 0.0191, OR = 1.0193, 95% CI: 0.1002 to 10.3239, $P < 0.05$; **Table 3**).

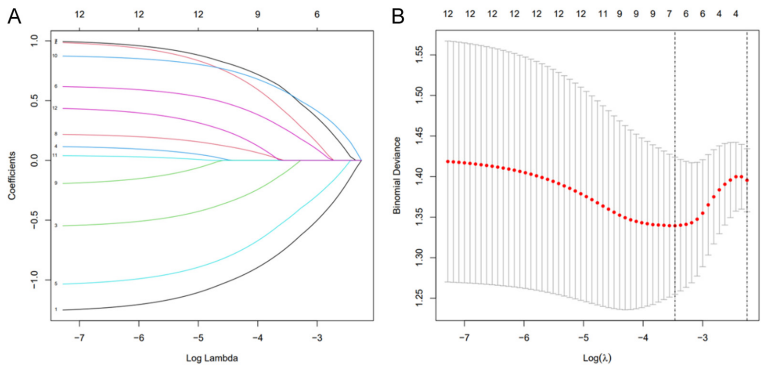

Figure 1. Screening factors using LASSO regression. A. Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log (lambda). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria). B. LASSO coefficient profiles of the 12 features. A coefficient profile plot was produced against the log (lambda) sequence. Vertical line was drawn at the value selected using fivefold cross-validation, where optimal lambda resulted in five features with nonzero coefficients. Abbreviations: LASSO, Least Absolute Shrinkage, and Selection Operator; SE, Standard Error.

Table 3. Predictors of nonadherence

Intercept and variable	*β*	OR (95% CI)	*P*-value
Intercept	0.0191	1.019 (0.100-10.323)	0.0231
Age	-1.2095	0.2984 (0.1132-0.7435)	0.0112
Sex	0.9133	2.4925 (0.7261-9.5999)	0.1594
Education level	-0.5044	0.6038 (0.3108-1.1389)	0.1242
Disease activity	-0.9523	0.3858 (0.1321-1.0523)	0.0697
Monthly income	0.5848	1.7946 (0.9878-3.3863)	0.0608
Medical insurance	1.0561	2.8752 (1.1433-7.6193)	0.0280
Adverse drug reactions	0.8973	2.4531 (0.9985-6.2406)	0.0534

β was the regression coefficient.

Nomogram

Based on the predictors of the LASSO regression analysis, a model containing these five independent predictors (age, disease activity, monthly income, medical insurance status, and adverse drug reactions) was developed and presented as a nomogram (**Figure 2**).

Accuracy of the prediction model

The calibration curves of the nomogram were used to predict the risk of medication nonadherence in RA patients, which exhibited good reliability (**Figure 3**). The C-index of the predicted nomogram was 0.759 (95% CI: 0.665-0.853), which was confirmed by 1,000 Bootstrap internal sampling validation (C-index of 0.726), indicating that the model had high discrimination ability. The ROC curve was constructed by multiple factors showing an area under the curve (AUC) of 0.7416, suggesting a high accuracy of this prediction model (**Figure 4**).

Clinical decision curve of the prediction model

The decision curve analysis showed that the predictive effect of the model could benefit about 75% of patients without harming other patients, suggesting a high net benefit and a safe and good clinical outcome (**Figure 5**).

Discussion

The main goal for the clinical treatment of the patients with RA is to stop the structural destruction of the joints and control the symptoms, thus preserving the function and working ability of the joints and improving the quality of life of the patients [17]. Nomograms have been widely used in oncology to predict the morbidity and prognosis of cancer patients. In addition, nomograms have helped healthcare professionals make better clinical decisions with a user-friendly and more easily understood digital interface [18, 19]. In this study, we used 5 clinical variables to develop and validate a new prediction tool which could predict the risk of biologic nonadherence in RA patients. The nomogram facilitated personalized prediction of biologic nonadherence in RA patients and identified patients with poor adherence so that an early intervention at the level of care could be implemented. The model was internally validated, and its C-index showed good discrimination and calibration capability. Among our study population, approximately 42% of patients were not adherent to biologic therapy, and the risk factor analysis showed that age, disease activity, monthly income, medical

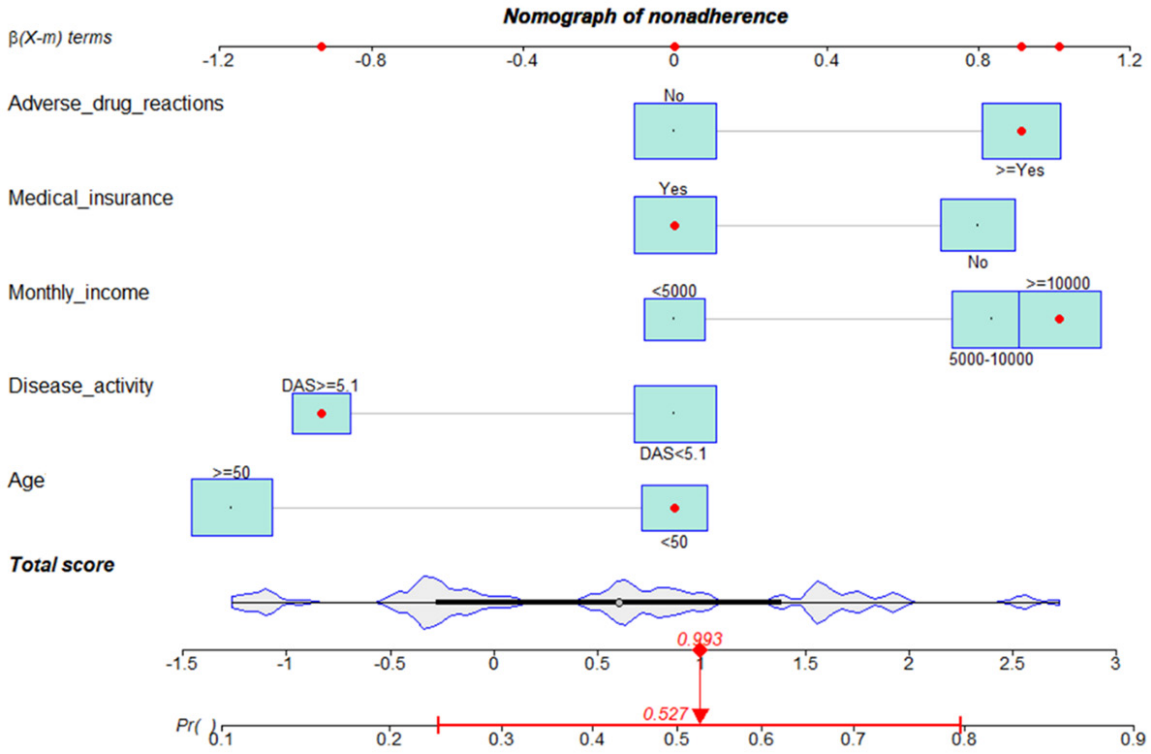

Figure 2. Nomograph of nonadherence. The medication nonadherence nomogram was developed in the cohort using 5 risk factors: age, disease activity, medical insurance status, monthly income, and disease activity.

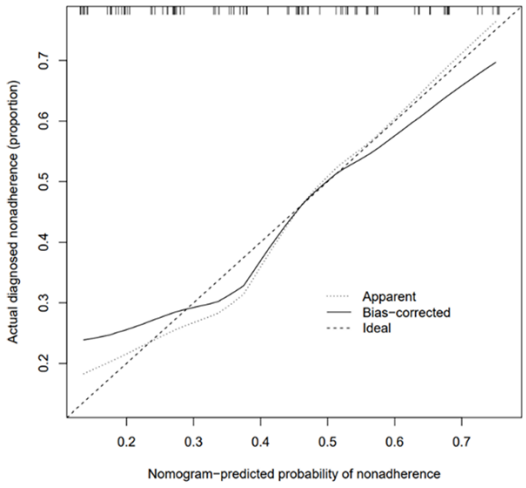

Figure 3. Calibration curves of the nonadherence nomogram prediction. The diagonal dotted line represented a perfect prediction by an ideal model, and the solid line represented the performance of our nomogram. A closer fit to the diagonal dotted line indicated a better prediction.

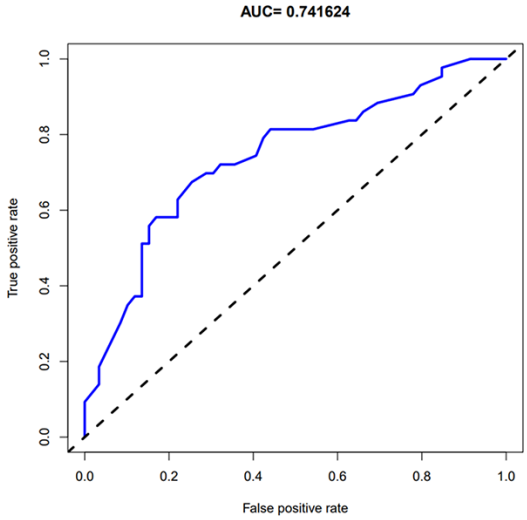

Figure 4. ROC curve of the prediction model. The ROC curve constructed by multiple risk factors showed an area under the curve (AUC) of 0.741624, suggesting a high accuracy of the prediction model.

insurance status, and adverse drug reactions were associated with medication adherence in patients with RA. This predictive model suggested that the above factors might be the risk factors in determining medication nonadherence in patients with RA.

Previous studies have shown that medication adherence affects the disease activity in RA

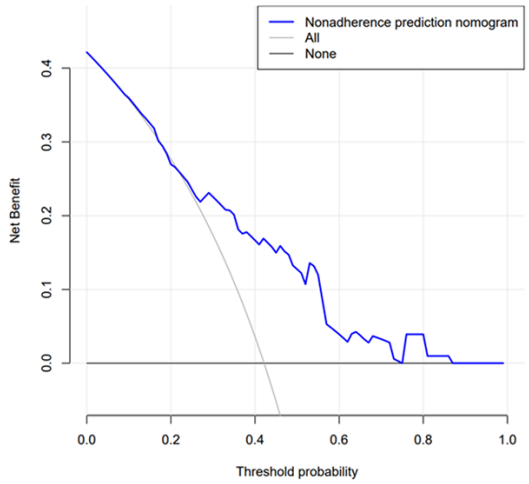

Figure 5. Decision curve analysis for the nonadherence nomogram. The decision curve of the prediction model was analyzed, and the "all" marked by the curve assumed that all patients comply. The curve marked "none" assumed that all patients do not comply.

patients, as RA patients with low medication adherence have a higher DAS28, whereas RA patients with higher adherence and more positive medication identity are associated with lower disease activity [17, 20, 21]. Similarly, our present study also showed that lower disease activity affected patients' adherence to biologics. In addition, Salaffi et al. reported a strong correlation between patients' medication nonadherence and low disease activity by logistic regression analysis of 209 RA patients treated with anti-TNF [22], which was consistent with our present study. The higher medication noncompliance in patients with low disease activity might reflect the fact that these patients tend to ignore the disease and are no longer willing to use biologics, which requires regular subcutaneous injection, once their disease is in remission. Therefore, clinical staff should pay more attention to the drug nonadherence in the patients with more stable disease control.

Similar to the results from previous studies [23, 24], older patients had poorer adherence to biologic agents, presumably because older patients have more comorbid diseases and psychological stress, and tend to lose confidence in continuing treatment if their symptoms do not resolve after a short period of treatment. In addition, economic income is closely related to the patient's medication nonadherence. When the World Health Organization evaluated the impact of out-of-pocket costs on the adherence of 2,285 RA patients to enalapam and adalimumab with more than 1 year of follow-up, a correlation between adherence and economic factors was found, in which the actual cost paid by patients was inversely related to adherence [25]. Furthermore, patients with out-of-pocket cost of more than $50 per week had higher risk (1.5 times) of discontinuing anti-tumor necrosis factor treatment compared to those with out-of-pocket cost of less than $50 per week (HR = 1.58, $P < 0.001$). Many patients often stop taking drugs because they do not work at the time of treatment or suffer from adverse drug reactions, leading to poor compliance and treatment failure [26].

Conclusion

In conclusion, we developed a nonadherence risk prediction nomogram which was simple to use and showed relatively good accuracy. It could be completed by nurses alone at the time of patient admission, which would help identify patients earlier with high risk of nonadherence so that timely interventions could be undertaken. Nevertheless, this study also had some limitations. First, our analysis of risk factors did not include all potential factors that might affect medication adherence, such as social support, occupation, and frequency of medication use. Second, although we tested the stability of the model through internal validation, external validation should be conducted with larger patient samples to determine whether an individual intervention based on this nomogram would reduce the risk of nonadherence.

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Disclosure of conflict of interest

None.

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