Predicting tophi formation risks amongst people with gout: a development and assessment of a new predictive model

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Abstract

Purpose: Tophi can cause several severe complications. However, the predictors of tophi formation are not intensively researched. The aim of the study is to develop and validate a new prediction model for tophi formation amongst patients with gout. Methods: A prediction model was developed using data collected from 158 gout patients treated in the inpatient department of The First Affiliated Hospital of Zhejiang Chinese Medical University from May 2018 to May 2020. For the establishment and validation of the prediction nomogram, the least absolute shrinkage and selection operator regression model and the multivariable logistic regression analysis were conducted to determine the predictors. C-index, calibration plot and decision curve analysis were utilised to evaluate discrimination, calibration and clinical effectiveness of the predicting nomogram. Then, the nomogram was internally validated using a bootstrap procedure. Results: Nine predictors – hospitalisation frequency, disease duration, number of joints involved in gouty arthritis, gout flares frequency, smoking, and whether combined with atherosclerosis, diabetes, hypertension and kidney dysfunction – were determined from the prediction nomogram. The C-index of the nomogram was 0.854 (95% confidence interval: 0.772-0.936), and was confirmed to be 0.810 when tested through a bootstrap validation, suggesting the model's good discrimination and prediction capability. Conclusion: A new model with nine predictors was developed to predict the risks of tophi formation amongst gout patients. The included predictors were practical and easy to obtain, whilst the nomogram was proved to predict the risks of tophi formation effectively and accurately. Keywords:tophi formation, gout, predictors, nomogram

Introduction

Gout is one of the most common inflammatory joint diseases, and is caused by an aberrant purine metabolism and a deposition of monosodium urate crystals (MSU) in and around the joints.[1] Its prevalence ranges from <1% to 6.8% amongst different races, and has shown an apparent rising and younger trend in recent years.[1] Tophi caused by a long-term deposition of MSU crystals is the characteristic symptom of advanced gout.[2] As reported, tophi develops in approximately 12-35% of gout patients.[3] However, the clinical significance of tophi is often underestimated. In fact, tophi may lead to several significant complications, such as irreversible joint deformities and dysfunctions, severely limited range of motions, bone destructions and even fractures.[4,5] Superficial tophi can cause infections and ulceration.[6] It can also cause entrapment neuropathy, such as carpal tunnel syndrome and radiculopathy.[7,8] The ideal treatment choice for patients with serious tophi complications is surgery, which has certain risks and may be quite expensive.[9] Overall, tophi seriously impacts the life quality and longevity of patients, not to mention a huge economic burden.[10]

Previous researches have indicated that multiple factors are related to tophi formation, including serum uric acid level, disease duration, age, gender, family history, gout flare frequency, incidence of obesity, hypertension, hyperlipidaemia, renal dysfunction, kidney stone, coronary heart disease, and upper limb joint involvement.[2,11,12] Considering the hazards of tophi, it is significant to establish an accurate prediction tool to confirm and evaluate the various influences of the above potential associated risk factors on tophi formation. This is likewise beneficial to the early prevention, diagnosis and treatment of tophi. However,

there are no relatively existing studies on this matter. Thus, this study was conducted to develop a simple yet valid prediction model to identify the predictors of tophi formation amongst people with gout.

Methods

Patients and Data Collection

The study subjects were patients diagnosed as 'gout' or 'gouty arthritis' in the electronic medical record system, and were treated in the inpatient department, of The First Affiliated Hospital of Zhejiang Chinese Medical University from May 2018 to May 2020. They came from all over Zhejiang province in China. They were deemed included if they had fulfilled the Gout Diagnostic Criteria formulated by the American College of Rheumatology (ACR)[13] or the 2015 Gout Classification Criteria by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR).[14] Patients diagnosed as secondary gout that caused by kidney or myeloproliferative diseases, or combined with other forms of arthritis such as osteoarthritis or rheumatoid arthritis were excluded. Tophi diagnosis was determined by rheumatologist or endocrinologist as draining or chalk-like subcutaneous nodules under transparent skin, often with overlying vascular and present around joints, ears, olecranon bursae, finger pads or tendons, based on the 2015 ACR/EULAR Gout Classification Criteria.[14] For patients who had been admitted to the hospital more than once during the study period, only the data from the first admission were analysed. Research approval was obtained from the hospital's Ethics Committee (approval no.2020-KL-127-01), and all study subjects were fully informed consents.

One hundred and fifty-eight gout patients were included in the study, and were classified as either 'tophi group' or 'non-tophi group' for analysis. Twenty-two variables, such as demographics and disease and treatment characteristics of the patients, were manually collected from the hospital's electronic medical record system **(Table 1)** . According to the result of a large sample size study of the clinical characteristics associated with Chinese tophaceous gout patients and previous clinical experience, we chose 45 years old, 10 years, 3 joints and 360 umol/l as respective cut point for onset age, disease duration, number of joint involved and serum uric acid level.[2]

Model Development and Validation

Considering its ability in both variable selection and shrinkage, the least absolute shrinkage and selection operator (LASSO) method was employed to select the optimal predictive factors of tophi formation from all variables.[15,16] All 22 variables were included in the LASSO model. Those variables with regression coefficients close to zero were excluded, with the remaining ones considered to be related to tophi formation. Additionally, the multivariable logistic regression model was also used to analyse the variables associated with tophi formation, and took those with P-value less than 0.05 as the possible predictors. Based on the aforementioned analyses and the results of previous clinical researches[2,11,12], nine candidate variables were eventually selected as the risk factors, and were applied for establishing a model for predicting the risks of tophi formation.[17,18] Afterward, the model's discrimination and calibration were correspondingly assessed using Harrell's concordance index (C-index) and a calibration curve. The C-index can reflect the consistency between the actual probability of the outcome and the predicted probability. It ranges between 0.5 and 1.0 and a higher C-index denotes a better accuracy of the prediction model. Meanwhile, by plotting a calibration curve, the relationship between the predicted probability (x-axis) and the observed probability of tophi (y-axis) was tested.

The model was validated by a bootstrap procedure that generates a large number of similar – but not entirely the same – data from the original dataset through random resampling with replacements.[19]A total of 1,000 bootstrap resamples were utilised to recalculate the relatively corrected C-index. If the corrected C-index is similar to the original value, then the model is deemed ideal due to its potential ability to perform similarly in different datasets. Meanwhile, the clinical practicability of the model was determined by a decision curve analysis that can quantify the net benefits at different threshold probabilities from the included patients' data.[20] The net benefit was calculated by subtracting the proportion of all false positive patients from those of true positive ones, and by weighing the relative harm of giving up interventions compared with the negative

consequences of unnecessary interventions.[21] All statistical analyses were performed using the R software, version 3.6.2 (https://www.R-project.org).

Results

Patients' Characteristics

A total of 158 patients were included in the final analysis. Depending on the presence or absence of tophi, they were divided into two groups. Twenty-nine patients were in the tophi group, and the rest in the non-tophi group. The 22 variables of patients, including the demographics and disease and treatment characteristics of the two groups, are shown in **Table 1** . It was found that the hospitalisation frequency, disease duration, number of joints involved in gouty arthritis and gout flares frequency were significantly elevated amongst tophi group patients than in the non-tophi group ($P<0.05$, **Table 1**). Likewise, there were more patients with atherosclerosis, diabetes, hypertension and kidney dysfunction in the tophi group than in the non-tophi group ($P<0.05$,**Table 1**).

Variable Selection and Model Development

Together with previous clinical researches, according to the results of the LASSO regression model and the multivariable logistic regression model, nine of the 22 variables were selected as the potential predictors of tophi formation (**Figures 1A and 1B**). These variables were hospitalisation frequency, disease duration, number of joints involved in gouty arthritis, gout flares frequency, smoking, and whether combined with atherosclerosis, diabetes, hypertension and kidney dysfunction. The logistic regression analysis results of these variables are shown in **Table 2** . A prediction model that contains the above predictors was then developed and represented as a nomogram (**Figure 2**).

Apparent Performance of the Tophi Formation Risk Nomogram

The calibration curve of the nomogram that predicts the risks of tophi formation amongst gout patients was demonstrated as having good agreement with the cohort (**Figure 3**). The C-index was 0.854 (95% CI: 0.772–0.936) for the cohort, and was confirmed to be 0.810 when tested in a bootstrap validation with 1,000 hypothetical datasets. This suggested the model's good discrimination and prediction capability.

Clinical Use

The decision curve analysis for the tophi formation risk nomogram is illustrated in **Figure 4** . The decision curve demonstrated that when the respective threshold probability for a patient and a doctor is 6.33% and 87.34, using the developed nomogram to predict tophi formation risks is more effective than the scheme. Within this range, the net benefit was comparable with several overlaps.

Discussion

A new prediction tool for the risks of tophi formation amongst gout patients was developed and validated in this study. The nomogram consisted of nine easily available variables, including hospitalisation frequency, disease duration, number of joints involved in gouty arthritis, gout flares frequency, smoking, and whether combined with atherosclerosis, diabetes, hypertension and kidney dysfunction. Through the analysis using C-index and calibration plot alongside internal verification, the nomogram was verified to have good discrimination and calibration ability, and could be widely used in gout patients to relatively accurately predict the risks of tophi formation.[22]

Based on the results of predictor analysis, the nomogram demonstrated that hospitalisation for more than twice per year, disease duration of more than ten years, more than three joints involved in gouty arthritis, frequency of gout flares for more than twice per year, smoking, and combined with atherosclerosis, diabetes, hypertension and kidney dysfunction could be the predictive factors for tophi formation. Amongst the nine risk factors, most were consistent with the results of previous studies.[2,23] A retrospective clinical study involving 5,693 Chinese gout patients depicted a significant difference ($P<0.05$) between the tophi and non-tophi groups with regard to disease duration (10.28 ± 7.54 years vs. 5.11 ± 6.06 years), number of joints

involved (3.11±2.15 vs. 1.81±1.35), systolic pressure (138.53±19.46 mmHg vs. 133.87±17.93 mmHg), diastolic pressure (89.55±12.73 mmHg vs. 87.48±11.77 mmHg) and creatinine clearance rate (Ccr) (93.05±48.7 mL/min vs. 106.61±51.76 mL/ min).[2]This study's results were similar to those findings, which might be explained by certain reasons. First of all, tophi is one of the manifestations of chronic gout as a deposition of uric acid crystals.[24] Similar to other chronic metabolic diseases, a longer gout duration entails more severe conditions, leading to more joints involved in gouty arthritis, more frequent gout flare and hospitalisation, as well as a higher probability of tophi formation. Secondly, previous studies have discussed that uric acid can increase blood pressure through damaging the vascular endothelium, activating the renin angiotensin aldosterone system, and reducing the nitric oxide levels in endothelium.[25] Meanwhile, hypertension can damage the renal blood perfusion and lead to tissue hypoxia, thus reducing the uric acid clearance rate. Therefore, a more severe gout leads to a higher risk of hypertension.[26] Likewise, a more serious hypertension denotes a more likelihood to cause kidney damage and a less excreted uric acid that entails a higher risk of tophi formation.[27] In addition, previous researches have indicated that smokers and diabetic patients have higher uric acid concentrations, which can lead to vascular endothelial dysfunction, thus increasing the risk of atherosclerosis, renal dysfunction and tophi formation.[28-30]

Based on the aforementioned risk factors, it is of great significance to enable certain measures to prevent and control tophi formation at an early stage. According to the nomogram, for patients with longer gout duration, apart from paying attention to controlling the blood uric acid level and reducing gout flare frequency as well as the number of joints involved in gouty arthritis, we should also highly consider monitoring blood glucose, blood pressure, renal function and vascular conditions in order to reduce the risks of tophi formation. For patients who already have the aforementioned risk factors, early diagnosis and treatment of tophi is necessary to avoid significant tophi-related complications such as irreversible joint deformity and dysfunction, bone destruction and fracture, infection and ulceration.

A series of steps had been undertaken to minimise potential bias in this study. Firstly, for patients who have been hospitalised more than once, only the data from the first hospitalisation were included to avoid inclusion of repeated cases. In the electronic medical record system, patients diagnosed with 'gout' or 'gouty arthritis' were searched using keywords or ICD codes to avoid missing patients, which might cause selection bias. Finally, uncertain data that were recorded in the hospital system were reconfirmed by contacting the patients to ensure data accuracy.

Despite the above measures, there are still some limitations in the current study. First of all, the sample size was relatively small; most subjects were male, and came from Zhejiang Province, China. Additionally, the sample size of the tophi group was small, which might limit the power of the regression analysis. Secondly, the predictive model might not have included all potential factors related to tophi formation. Since all data were collected from medical records of discharged patients during hospitalization, some variables such as serum uric acid and body mass index, might not represent patients' actual uric acid and weight control. Besides, certain demographics such as family history and smoking or drinking history might be inconsistent with the actual situation, due to patients' intentional concealment or unintentional false memories. Thirdly, despite the efforts to examine the robustness of the nomogram by internal verification using a bootstrap test, it is still possible that the nomogram is not quite useful for gout populations in other regions and countries. Hence, an external validation in wider populations is necessary in future studies.

Conclusion

This study developed a new model to help clinicians identify gout patients who are at risk of tophi formation. The proposed predictive factors were practical, non-invasive and easily obtainable. Through an assessment of individual risks, the model may help doctors and patients to enable more active and effective measures regarding tophi prevention and treatment. However, due to lack of a large sample size and external verification, further studies are still required to verify the nomogram's validity and accuracy.

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Conflict of interest

The authors declare no conflict of interest.

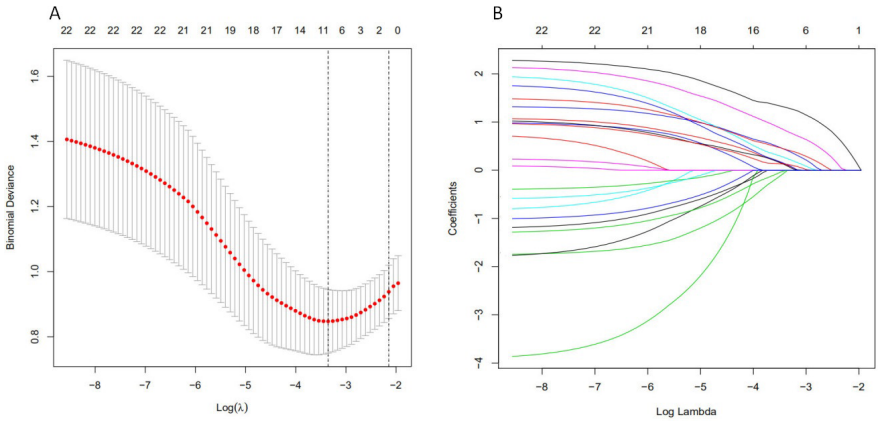
Table 1 Differences between demographic and clinical characteristics of tophi and nontophi groups	**Table 1 Differences between demographic and clinical characteristics of tophi and nontophi groups**	**Table 1 Differences between demographic and clinical characteristics of tophi and nontophi groups**	**Table 1 Differences between demographic and clinical characteristics of tophi and nontophi groups**
Demographic characteristics	**n (%)**	**n (%)**	
	tophi (n=29)	**non-tophi(n=129)**	**P-value**
Onset age (years)	46.97±14.90	46.39±16.66	0.86
Hospitalization frequency (per year)	1.59±0.87	1.23±0.79	0.03
Disease duration (years)	16.48±10.91	8.20±5.98	¡0.0001
BMI(kg/m^2)	24.05±3.56	25.52±3.70	0.053

Number of Joints involved	4.14±2.72	2.52±1.32	<0.0001
Serum uric acid(umol/l)	477.30±141.60	516.40±129.60	0.15
Gender			0.91
Female	1(3.45)	5(3.88)	
Male	28(96.55)	124(96.12)	
Marital status			0.56
Married	28(96.55)	121(93.80)	
Other marital statuses	1(3.45)	8(6.20)	
Employment			0.94
Employed	20(68.97)	88(68.22)	
Unemployed	9(31.03)	41(31.78)	
medical insurance			0.30
rural cooperative or urban medical insurance	27(3.45)	111(86.05)	
self-funded	2(96.55)	18(13.95)	
Diabetes			0.03
Yes	1(3.45)	5(3.88)	
No	28(96.55)	124(96.12)	
Hypertension			0.008
Yes	22(75.86)	63(48.84)	
No	7(24.14)	66(51.16)	
Atherosclerosis			0.027
Yes	7(24.14)	12(9.30)	
No	22(75.86)	117(90.70)	
Hyperlipidemia			0.61
Yes	10(34.48)	51(39.53)	
No	19(65.52)	78(60.47)	
Kidney dysfunction			0.028
Yes	16(55.17)	43(33.33)	
No	13(44.83)	86(66.67)	
Urinary tract stone			0.76
Yes	11(37.93)	45(34.88)	
No	18(62.07)	84(65.12)	
Family history			0.24
Yes	1(3.45)	13(10.08)	
No	28(96.55)	116(89.92)	
(Continued)	**(Continued)**	**(Continued)**	**(Continued)**
Table 1 (Continued)	**Table 1 (Continued)**	**Table 1 (Continued)**	**Table 1 (Continued)**
Demographic characteristics	**n (%)**	**n (%)**	
	tophi (n=29)	**non-tophi(n=129)**	**P-value**
Smoking			0.11
Yes	12(41.38)	34(26.36)	
No	17(58.62)	95(73.64)	
Drinking			0.42
Yes	11(37.93)	39(30.23)	
No	18(62.07)	90(69.77)	

Gout flares frequency(per year)			0.031
¡2	1(3.45)	26(3.88)	
[?]2	28(96.55)	103(96.12)	
Urate lowering therapy			0.26
Yes	4(13.79)	30(23.26)	
No	25(86.21)	99(76.74)	
Use of GC			0.46
Yes	12(41.38)	44(34.11)	
No	17(58.62)	85(65.89)	

Table 2 Prediction factors for tophi formation **Intercept and variable**	**Table 2** Prediction factors for tophi formation **Prediction model**	**Table 2** Prediction factors for tophi formation **Prediction model**	**Table 2** Prediction factors for tophi formation **Prediction model**
	β	**Odds ratio (95% CI)**	**P-vaule**
Hypertension	1.98	7.28(1.58-45.37)	0.019
Diabetes	1.33	3.78(0.85-18.48)	0.086
Smoking	1.79	6.00(1.32-32.14)	0.026
Disease duration>=10	2.30	9.95(1.76-52.28)	0.019
Number of Joints involved>=3	1.50	4.49(1.10-22.65)	0.048
Kidney dysfunction	0.99	2.69(0.63-12.64)	0.189
Gout flares frequency>=2	1.05	2.85(0.28-79.93)	0.438
Atherosclerosis	1.09	2.97(0.62-15.09)	0.174
Note: β is the regression coefficient. **Abbreviations:** CI, confidence interval.	**Note:** β is the regression coefficient. **Abbreviations:** CI, confidence interval.	**Note:** β is the regression coefficient. **Abbreviations:** CI, confidence interval.	**Note:** β is the regression coefficient. **Abbreviations:** CI, confidence interval.

Figure 1 Demographic and clinical feature selection using the LASSO binary logistic regression model



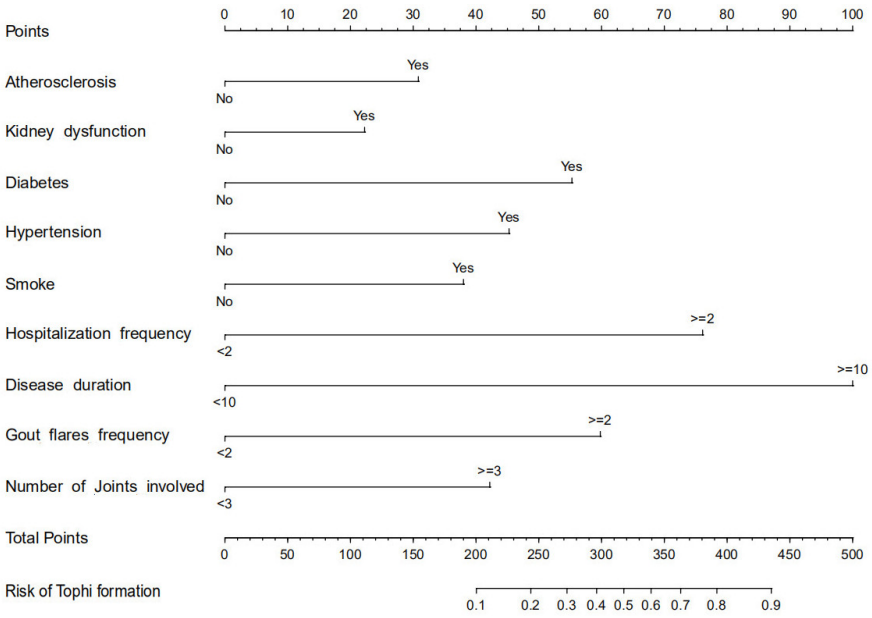
Notes: (A) Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation via

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 22 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.

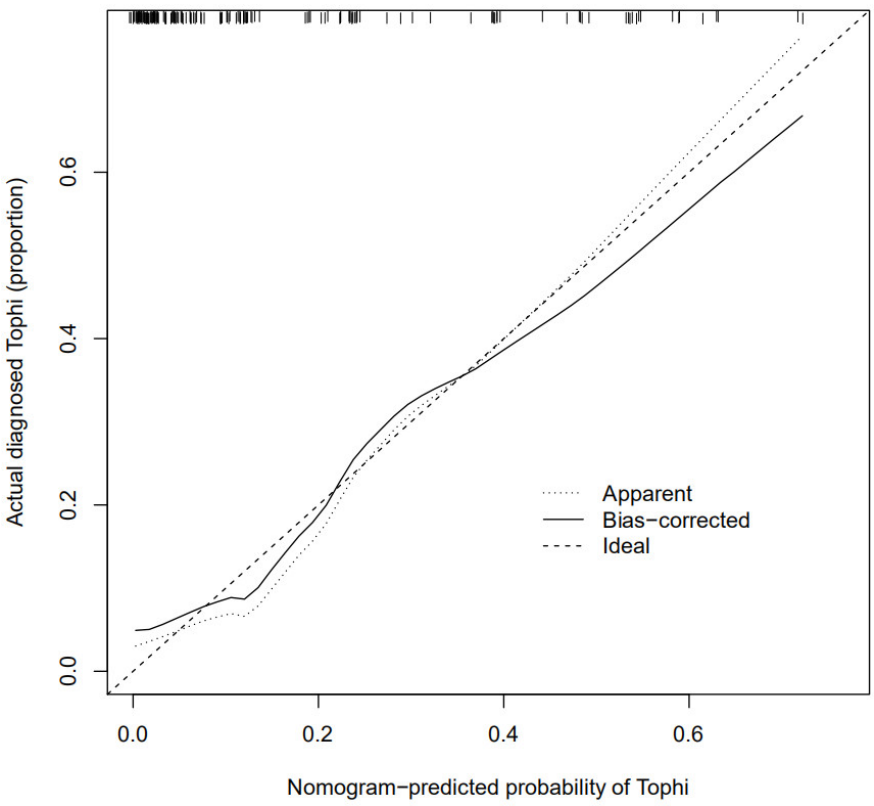
Abbreviations: LASSO, least absolute shrinkage and selection operator; SE, standard error.

Figure 2 Developed tophi formation risk prediction nomogram



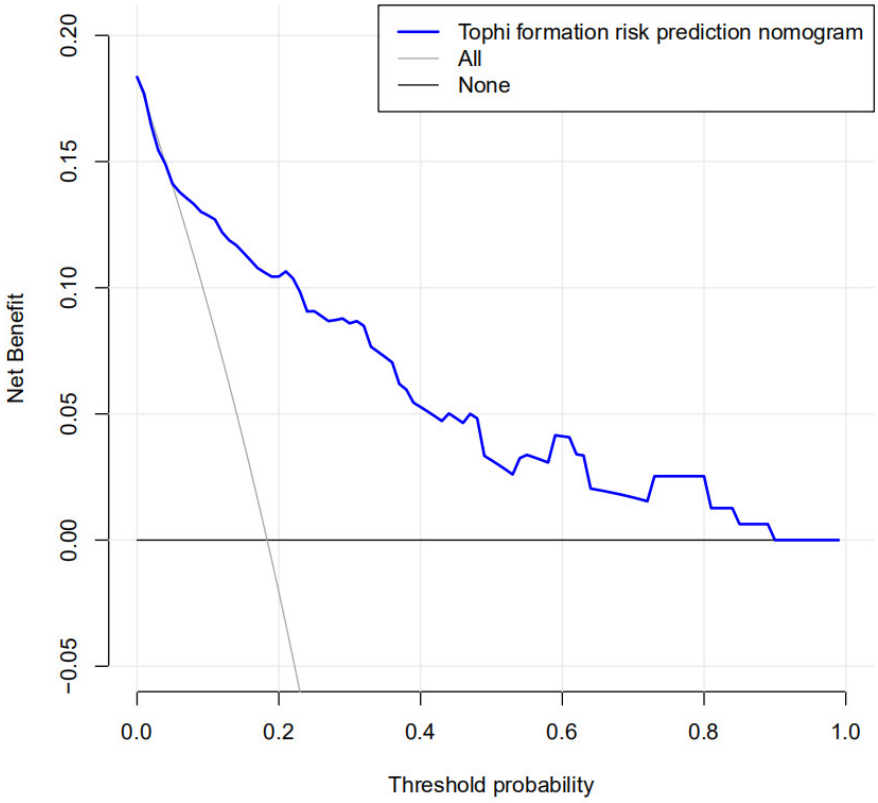
Notes: The tophi formation risk prediction nomogram was developed in the cohort, with hospitalization frequency, disease duration, number of Joints involved, gout flares frequency, whether smoke and combined with atherosclerosis, diabetes, hypertension and kidney dysfunction.

Figure 3 calibration curves of the tophi formation risk prediction nomogram in the cohort



Notes: The x-axis represents the predicted tophi formation risk. The y-axis represents the actual diagnosed tophi. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction.

Figure 4 Decision curve analysis for the tophi formation risk prediction nomogram



Notes: The y-axis measures the net benefit. The dotted line represents the tophi formation risk prediction nomogram. The thin solid line represents the assumption that all patients have tophi formed. Thin thick solid line represents the assumption that no patients have tophi formed. The decision curve showed that if the threshold probability of a patient and a doctor is 6.33% and 87.34%, respectively, using this nomogram in the current study to predict tophi formation risk adds more benefit than the intervention-all-patients scheme or the intervention-none scheme.