Article

Discovery Medicine 2023; 35(177): 517–524
https://doi.org/10.24976/Discov.Med.202335177.52

Using Machine Learning to Identify Risk Factors and Establishing a Clinical Prediction Model to Predict Atherosclerosis Complications in Idiopathic Membranous Nephropathy

Yipeng Chen[1,†], Ying He[2,†], Guangqun Xing[1,*]

[1]Department of Nephropathy, Affiliated Hospital of Qingdao University, 266003 Qingdao, Shandong, China
[2]Department of Pediatric Surgery, Affiliated Hospital of Qingdao University, 266003 Qingdao, Shandong, China
*Correspondence: gqx99monash@163.com (Guangqun Xing)
[†]These authors contributed equally.
Published: 1 August 2023

Background: Clinically, it has been observed that patients with idiopathic membranous nephropathy (IMN) have a higher probability of coronary heart disease. We aim to investigate the risk factors associated with coronary heart disease in IMN patients using a mechanomics approach and establish a clinical diagnosis model.

Methods: We collected sixty-nine clinical data points from patients undergoing phospholipase A2 receptor (anti-PLA2R) tests at the Affiliated Hospital of Qingdao University between July 9, 2019 and March 15, 2021. We excluded patients with cancer, hepatitis B, recent injuries or surgeries, and those under 18. Finally, 162 patients were considered for our study, which included 73 patients with coronary heart disease. The patients were split into test and validation groups at a 7:3 ratio. We utilized the Mann-Whitney U test for initial factor screening and the least absolute shrinkage and selection operator (LASSO) regression for further index screening. Eventually, the effectiveness of the clinical model was evaluated through visual statistical methods.

Results: Age, lymphocyte count, the sum of high-density lipoprotein (HDL) and low-density lipoprotein (LDL), serum creatinine, and antithrombin III were risk factors for coronary heart disease in patients with idiopathic membranous nephropathy in a multivariate regression ($p < 0.1$). In the training group, 14 clinical features were finally screened by the LASSO regression, and the area under the curve (AUC) of the training group was 0.90 (95% CI 0.877–0.959), accuracy (ACC) was 0.85, sensitivity was 0.76, specificity was 0.91, and precision was 0.85. F1 scored 0.80. In the verification group, AUC was 0.84 (0.743–0.927), ACC was 0.80, sensitivity was 0.67, specificity was 0.87, precision was 0.75, and F1 scored 0.71. We then visualized them using a nomogram based on multivariate regression. The C index and clinical decision curve evaluated them. The C index was 83.8%, and the clinical decision curve was also excellent.

Conclusions: We've established an effective clinical prediction model for patients with IMN who also have coronary heart disease. This model holds significant potential for enhancing clinical decision-making.

Keywords: idiopathic membranous nephropathy (IMN); atherosclerosis (AS); prediction model; machine learning

Introduction

Idiopathic membranous nephropathy (IMN) is a prevalent cause of nephrotic syndrome among adults. This disease is an organ-specific autoimmune disorder that impacts the glomeruli in the kidneys, characterized by subcutaneous immune deposits [1,2]. The primary autoantigen involved in IMN is the M-type phospholipase A2 receptor (PLA2R). This receptor protein is expressed in human podocytes and aligns with *IgG4* in subepithelial immune deposits [2]. Notably, circulating anti-PLA2R autoantibodies are found in approximately 70% of patients with IMN. As such, these antibodies have rapidly become an essential biomarker in clinical settings, aiding in the diagnosis, treatment, and prognosis evaluation of IMN [3–7].

Atherosclerosis (AS) is believed to be an autoimmune condition. To date, researchers have identified three proteins that serve as AS autoantibodies: heat shock proteins (HSPs), oxidized low-density lipoprotein (ox-LDL), and β2 glycoprotein 1 (β2GP1) [8]. AS is a progressive disease that can lead to arterial thrombosis, calcification, etc. [8]. Some studies have shown that chronic kidney disease (CKD) is one of the risk factors for AS [9]. Radhakrishnan [10] demonstrated that patients with nephrotic syndrome have lipid abnormalities that are risk factors for AS compared with normal subjects. The secretory phospholipase A2 (sPLA2) is thought to be involved in the pathogenesis of AS [11]. Meanwhile, IMN is the immune nephropathy caused by anti-PLA2R. Clinically, we observed that patients with IMN combined with AS were higher than the

general population. Herein, we conducted this study to explore risk factors of IMN complicated with AS.

Machine learning has emerged in recent years as a revolutionary method for statistical data analysis. It is renowned for its high efficiency and accuracy, and human factors do not readily influence its analyses [12]. In our clinical practice, we've observed a high AS incidence among patients with IMN. This correlation is rarely mentioned in prior studies, likely due to the substantial interference among data in clinical studies. By employing mechanomics, we can mitigate this interference to a certain extent, hence our choice to utilize this method. Therefore, this study aims to employ machine learning techniques to explore the risk factors that associate IMN with AS and, subsequently, to develop a relevant clinical model.

Materials and Methods

Study Participants

This retrospective study was conducted in the Affiliated Hospital of Qingdao University. Clinical data of patients tested for serum anti-PLA2R in the Affiliated Hospital of Qingdao University between July 9, 2019 and March 15, 2021, were collected. There were multiple measurements with the highest titer included in the analysis. Inclusion criteria were defined as having clear pathological support or serum anti-PLA2R titer greater than 20 RU/mL. Patients with cancer, hepatitis B, recent injuries or surgeries, and those under 18 were excluded. In the end, 162 patients were included, among which 73 patients with AS accounted for 44.79% of the total. According to the ratio of 7:3, the patients were divided to training queue and the verification queue. The training group is used to train the model, and the validation group data is used to determine the prediction efficiency of the model (Fig. 1). A comparison of basic clinical data between the training and validation cohorts is shown in Table 1.

Serum Anti-PLA2R Antibodies Titer Determination

All serum samples underwent testing for anti-PLA2R IgG antibodies utilizing a quantitative ELISA (Euroimmun, Luebeck, Germany). The process was conducted in strict adherence to the manufacturer's guidelines. Interpretation of the results, according to the manufacturer's instructions, was as follows: a result less than 14 RU/mL was considered negative, a result from 14 to just under 20 RU/mL was categorized as borderline, and a result of 20 RU/mL or higher was determined as positive.

Clinical Data Collection

The initial clinical data for this study were collected from the comprehensive examination that patients underwent upon admission, and these data were sourced from the electronic medical record system of the Affiliated Hospital of Qingdao University. We assembled a set of 69 clinical markers for each patient enrolled in the study. These markers, primarily derived from hematological assessments, encompassed various dimensions, including renal, liver, cardiac, and coagulation functions.

Feature Selection and Model Construction

We initially evaluated if the data distribution for IMN patients, both with and without AS in the training group, adhered to a normal distribution. The data distribution of the two groups of patients did not conform to the normal distribution after examination and analysis, so we used the Mann-Whitney U test for feature screening based on the data distribution characteristics of the training group. After the U test, the variance selection method was used to screen further the clinical features affecting patients with atherosclerosis. Clinical factors exhibiting low correlation were removed on the basis of the optimal threshold. Subsequently, we employed the least absolute shrinkage and selection operator (LASSO) regression algorithm to identify risk factors associated with AS. We implemented a 10-fold cross-validation approach to prevent overfitting of the model. A logistic regression model was constructed to observe the predictive efficacy of clinical risk factors in patients with idiopathic membranous nephropathy complicated with atherosclerosis, and the receiver operating characteristic curve (ROC) was drawn. We used accuracy (ACC), sensitivity, specificity, precision, F1-score, and area under the curve (AUC) value to evaluate the model's predictive performance. Validation group data is used to verify the predictive performance of the model.

Nomogram Construction

We carried out a multifactor analysis on the features screened (Table 2), including the features with a p value less than 0.1 in the multifactor results into the nomogram, and used the calibration curve to evaluate the consistency of the nomogram model. In addition, decision curve analysis (DCA) was used to quantify the probability of net benefit and assess its clinical value.

Statistical Analysis

Descriptive statistics, Pearson χ^2 test, and logistic regression model were calculated using SPSS 25.0 (IBM Corp, Armonk, NY, USA) nomogram, C-index and clinical decision curve were performed using R software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). LASSO uses Python (version 3.6, Python Software Foundation, Beaverton, USA). The 'RMS' and 'RMDA' packages in R were utilized to obtain the nomogram and decision curve, respectively. A p value of less than 0.01 was considered statistically significant.

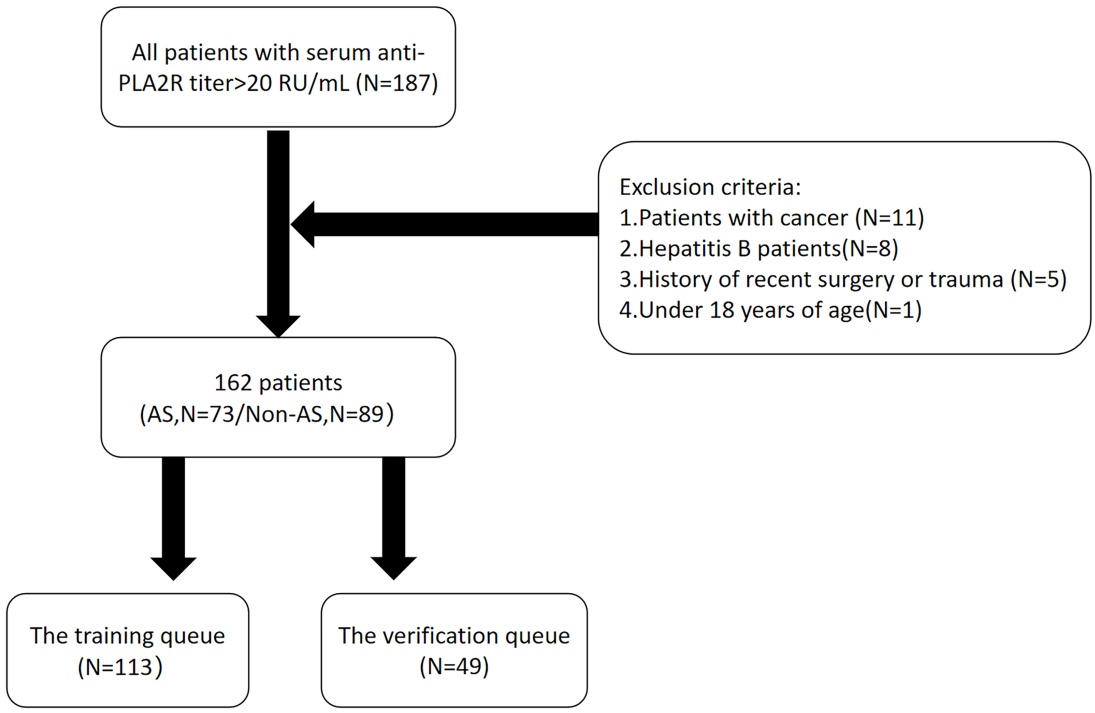

Fig. 1. The flowchart of patients selection.

Results

In the end, we selected 14 clinical features for our study. The process of feature selection via the LASSO regression algorithm is depicted in Fig. 2. Additionally, we present the proportion of the selected features (Fig. 3A) and a correlation heat map between these features (Fig. 3B). The training group yielded an AUC of 0.90 (95% CI, 0.877–0.959), an ACC of 0.85, a sensitivity of 0.76, a specificity of 0.91, and a precision of 0.85, with an F1-score of 0.80. For the validation group, the AUC was 0.84 (0.743–0.927), ACC was 0.80, sensitivity was 0.67, specificity was 0.87, precision was 0.75, with an F1-score of 0.71, as illustrated in Fig. 4.

Clinical risk factors with a p value less than 0.1 in multivariate analysis included Age, lymphocyte (LYM), high density lipoprotein (HDL)+low density lipoprotein (LDL), Serum creatinine (SCR), and blood coagulation factor III (AT-III). A nomogram was developed based on these five features to predict IMN with AS (Fig. 5). The nomogram shows the different values of each variable. The corresponding integral (default: 0~100 points) is obtained by a vertical line on the scoring scale at the top of the nomogram. Then, the integral of all variables is added to the total score, and the corresponding forecast risk value is obtained by the total score line on the prediction line at the bottom of the nomogram. The calibration curve demonstrates excellent consistency in the nomogram model. Furthermore, the DCA (Fig. 6) suggests that the model yields substantial net benefits when the threshold probability ranges between 0.2 and 0.4. This indicates that the prediction model offers high levels of safety and substantial clinical application value.

Discussion

Traditionally, IMN was perceived as a condition predominantly affecting older people [13], as was AS. Consequently, studies investigating AS in IMN patients, especially concerning renal factors, should have been more noticed. However, with the incidence of IMN now observed in younger populations, the prominence of AS as a complication has increased significantly. In line with our pre-existing understanding, this study confirms that age continues to be a risk factor for AS in patients with IMN [8,14].

In this study, we apply the mechanomics logistic regression model, a classic model frequently employed to address clinically relevant issues. In Fig. 2, 69 indicators were selected based on the LASSO regression algorithm, and 14 clinical features were finally selected. In addition, in Fig. 4, the AUC of the training cohort was 0.90 (95% CI 0.877–0.959), ACC was 0.85, sensitivity was 0.76, specificity was 0.91, and precision was 0.85. F1 scored 0.80. In the validation cohort, AUC was 0.84 (0.743–0.927), ACC was 0.80, sensitivity was 0.67, specificity was 0.87, precision was 0.75, and F1 scored 0.71. It shows that the performance of this model is reasonable under the mechanical learning algorithm.

Higher LDL and lower HDL levels are recognized risk factors for AS [8]. Previous studies have not identified HDL+LDL as a single factor, largely due to multicollinearity with LDL and HDL when analyzed in traditional re-

Table 1. Comparison of basic clinical data between training and validation cohorts.

Characteristics	Training cohort (N = 113)	Validation cohort (N = 49)	*p* value	χ^2 value/Z
Age (years)	53.00 (42.00, 63.00)	52.00 (44.50, 59.00)	0.597	–0.529
Gender (%)			0.302	1.064
Male	64 (56.64%)	32 (65.31%)		
Female	49 (43.36%)	17 (34.69%)		
BMI (kg/m^2)	25.40 (23.38, 27.88)	25.15 (22.80, 26.93)	0.379	–0.879
SBP (mmHg)	138.00 (124.00, 153.5)	137.00 (127.00, 152.50)	0.825	–0.221
DBP (mmHg)	81.00 (73.00, 91.50)	83.00 (73.00, 94.50)	0.567	–0.573
Anti-PLA2R (RU/mL)	65.74 (23.32, 211.68)	40.6 (29.18, 98.16)	0.333	–0.968
Smoking (%)			0.277	1.183
Present	19 (16.81%)	5 (10.20%)		
Absent	94 (83.19%)	44 (89.80%)		
Alcohol abuse (%)			0.061	3.515
Present	16 (14.16%)	2 (4.08%)		
Absent	97 (85.84%)	47 (95.92%)		
Diabetes (%)			0.621	0.244
Present	13 (11.50%)	7 (14.29%)		
Absent	100 (88.50%)	42 (85.71%)		
Hyperuricemia (%)			0.927	0.008
Present	11 (9.73%)	5 (10.20%)		
Absent	102 (90.27%)	44 (89.80%)		
AS (%)			0.710	0.138
Present	52 (46.02%)	21 (42.86%)		
Absent	61 (54.98%)	28 (57.14%)		

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PLA2R, phospholipase A2 receptor; AS, atherosclerosis.

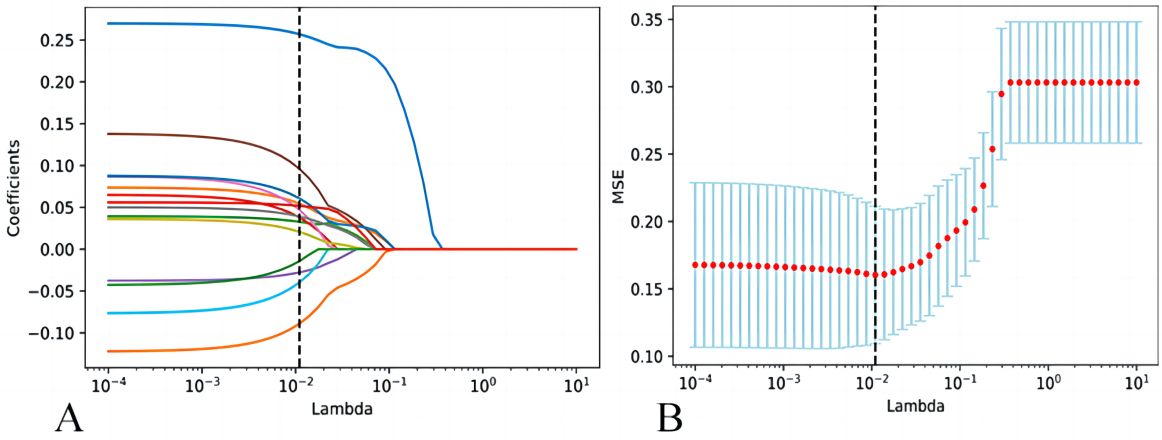

Fig. 2. Diagram showing convergence of feature selection coefficient in the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm. (A) Curves with different colors represent changes in different independent variables. With the increase of parameter log (λ), the variable of independent coefficient gradually tends to 0. (B) 10-fold cross-validation was used to select the optimal λ, and the parameter values corresponding to the vertical dotted line in the left figure were taken in this study.

search contexts. However, by utilizing the LASSO regression method, we are now able to safely incorporate these indicators into the equation, yielding cleaner metrics. In clinical practice, an HDL reference value typically hovers at 1.0 mmol/L, with the LDL reference value falling below 3.2 mmol/L. The LDL+HDL index offers a more intuitive representation of a patient's abnormal lipid metabolism, indicating a disruption in their lipid balance. Recent studies on lipid oxidation products (LOPs) have begun to explore the interrelation between LDL and HDL. LDL is an active carrier of LOPs to peripheral tissues, while HDL is active in reverse transport [15]. Moreover, AS is often perceived as a chronic inflammatory response, with LDL playing a significant role in oxidative stress [16].

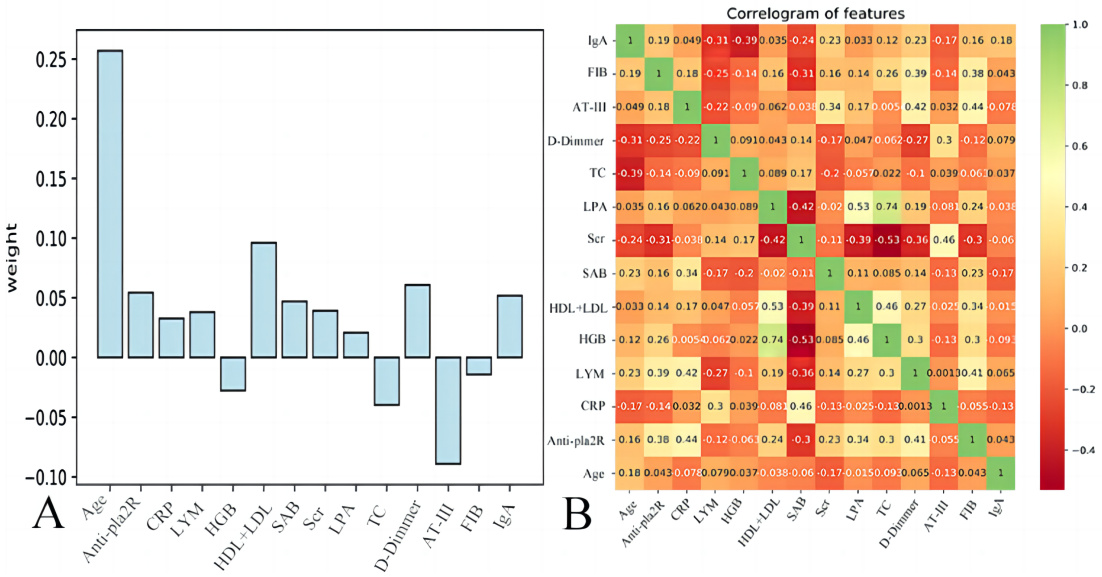

Fig. 3. The LASSO regression results of training cohort. (A) Features weight analysis diagram. (B) Feature correlation heat map.

Table 2. Multivariate analysis of factors after the Least Absolute Shrinkage and Selection Operator (LASSO) regression screening in training cohorts.

	B	*OR*	*95% CI*	*p* value
Age	0.191	1.21	1.106–1.324	0.001
Anti-PLA2R	0.001	1.001	0.998–1.004	0.346
CRP	0.07	1.073	0.882–1.305	0.483
LYM	0.736	2.008	0.871–5.001	0.099
HGB	–0.032	0.969	0.932–1.007	0.108
HDL+LDL	0.86	2.363	1.039–5.373	0.040
SAB	0.104	1.109	0.956–1.287	0.170
SCR	0.055	1.057	0.998–1.119	0.059
LPA	0.001	1.001	0.998–1.003	0.513
TC	–0.428	0.652	0.368–1.152	0.141
D-Dimmer	0.001	1.001	0.999–1.002	0.317
AT-III	–0.091	0.913	0.856–0.974	0.006
FIB	–0.334	0.716	0.295–1.737	0.460
IgA	0.598	1.818	0.748–4.422	0.187

CRP, c-reactive protein; HDL, high density lipoprotein; HGB, hemoglobin; LDL, low density lipoprotein; LPA, lipoprotein(a); LYM, lymphocyte; SAB, serum albumin; SCR, serum creatinine; TC, total cholesterol; AT-III, blood coagulation factor III; FIB, fibrinogen; IgA, immunoglobulin A.

This study discovered an independent association between AT-III and AS, where AT-III serves as a protective factor, a finding that corroborates H Bukowska's observations [17]. AT-III, an essential coagulation factor in endogenous coagulation [18], along with D-Dimer and plasma fibrinogen (FIB), were all identified as crucial factors through the LASSO regression. They exhibit multicollinearity independent of other factors. Notably, these three indicators are associated with the occurrence of thromboembolism.

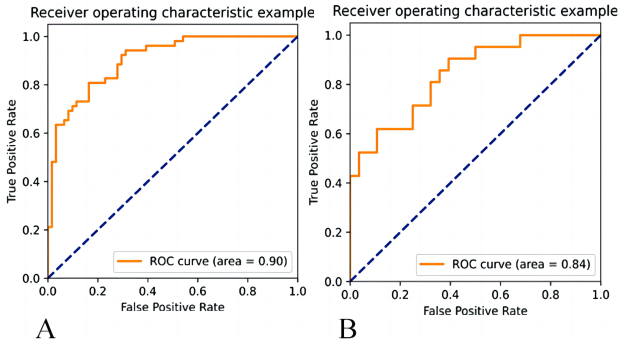

Fig. 4. Receiver operating characteristic curve (ROC) comparison of the training and validation cohort. (A) Training cohort. (B) Validation cohort (Using Python 3.6 software, following the principle of randomization, 162 patients were divided into a training cohort (n = 73) and a validation cohort (n = 49) at a ratio of 7:3).

Atherosclerosis can evolve into arterial thromboembolism (ATE), a dynamic process [8]. Clinically, a thrombus's size, location, and presence are typically confirmed via imaging tests. However, these tests only reveal clots beyond a certain size. The significance of these three coagulation indices may not be fully explained by the pathogenesis of AS alone. Our research team posits that these indicators suggest a transformation of AS into ATE in patients with IMN complicated with AS and the activation of the human coagulation system. Thromboembolism is one of the major complications of IMN and can manifest in the early stages. Historically, venous thrombosis (VTE) has been mainly reported [19]. However, Pei-Mei Zou *et al*'s work [20] suggests that ATE is also prevalent in IMN cases, albeit a relatively newer finding.

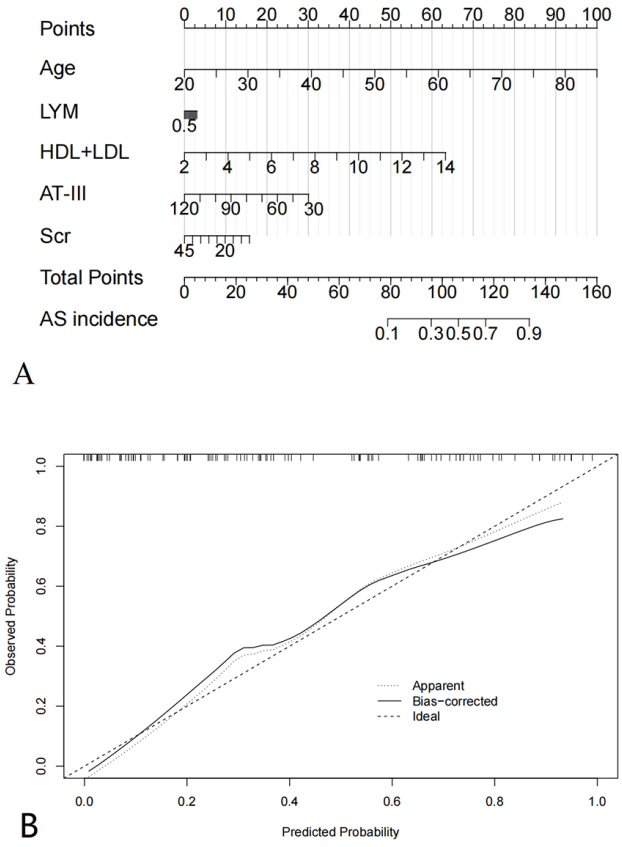

Fig. 5. A visual clinical prediction model was constructed and verified. (A) Nomogram for the prediction for.idiopathic membranous nephropathy complicated with atherosclerosis. (B) Calibration curves for nomogram.

The specific antibody to IMN is anti-PLA2R, which is IgG4 [2]. Anti-PLA2R markers provide important guidance in the diagnosis and prognosis of membranous nephropathy, as well as the outcome of the disease [21,22]. In Table 2, this factor has little significance. Most studies have shown that this factor is a composite variable associated with the disease status of IMN [6]. To some extent, anti-PLA2R is not linear with S-PLA2 [23]. The disease course of IMN is generally not accompanied by abnormal serum immunoglobulin A (IgA) content. The heat shock protein IgA increases the risk of switching to AS in patients with autoimmune diseases [24]. SCR is another factor associated with kidney disease. This factor was successfully screened in the LASSO regression. In Table 2, this factor performs well, and the trace is incorporated into the model in Fig. 3A. The inclusion of SCR directly indicates the current renal function in IMN patients. This effectively establishes an intuitive connection between IMN and AS.

Total cholesterol (TC) and lipoprotein(a) (LPA) are traditionally recognized risk factors for AS [25–27]. However, in the context of IMN, these common AS risk factors don't appear to be specific. To understand this, we need to examine LPA metabolism. Produced by the liver and metabolized by the kidneys [28], LPA accumulates when renal filtration function decreases, leading to elevated blood LPA levels. Concurrently, certain studies suggest that hypercholesterolemia does not lead to AS in nephrotic syndrome, aligning with our study's findings [29].

We included 5 factors less than 0.1 to build the histogram. C index indicates that in the case of 1000 self-sampling times, there are 162 errors, and the prediction rate is 83.8%. It can be seen from Fig. 5B that the predicted line is close to the actual line, indicating that the model has good prediction performance. In Fig. 6, we use DCA to test the net income of the model. The area under the curve represents the net income. The larger the area, the better the net benefit of the model. With the evidence of the DCA and C index, we know that Fig. 5A has a better clinical prediction effect and greater clinical decision-making benefit value, which can better serve the clinic. However, the clinical prediction model still needs to be improved. In the future, we will expand the samples and collaborate with multiple research centers to improve the project.

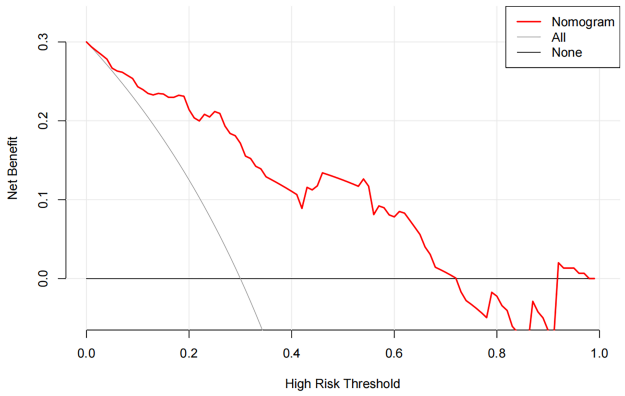

Fig. 6. The decision curve analysis results are presented to predict Idiopathic membranous nephropathy (IMN) complicated with Atherosclerosis (AS). The graph's x-axis represents the threshold probability, while the y-axis denotes the net benefit. A model is considered more meaningful when the area under the curve (AUC), formed the curve along with all and none lines, is larger.

This study offers Fig. 5A as an essential clinical tool that provides valuable guidance in clinical practice. Clinicians can swiftly gauge the probability of AS complications in IMN patients by utilizing this tool after admitting IMN patients and performing the initial assessment. By confirming the presence of AS through relevant examinations, clinicians can proceed with appropriate preventive measures.

Conclusions

In this study, our primary focus was on the incidence of AS in IMN patients, resulting in the successful devel-

opment of a predictive model. However, we acknowledge certain limitations in our approach. Firstly, this was a single-center study with a relatively homogeneous demographic regarding geographical location and race. Secondly, it was a retrospective study, which inherently carries potential bias. Despite these limitations, we created an effective clinical prediction model on the basis of mechanomics that can predict coronary heart disease in patients with IMN.

Abbreviations

ACC, accuracy; AS, atherosclerosis; AT-III, blood coagulation factor III; AUC, area under the curve; BMI, body mass Index; CKD, chronic kidney disease; CRP, c-reactive protein; DBP, diastolic blood pressure; FIB, fibrinogen; HDL, high density lipoprotein; HGB, hemoglobin; HSPs, heat shock protein; IMN, idiopathic membranous nephropathy; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; LPA, lipoprotein(a); LYM, lymphocyte; ox-LDL, oxidized low-density lipoprotein; PLA2R, phospholipase A2 receptor; ROC, receiver operating characteristic curve; SAB, serum albumin; SBP, systolic blood pressure; SCR, serum creatinine; sPLA2, secretory phospholipase A2; TC, total cholesterol; β2GP1, β2 glycoprotein 1.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

Concept and design: YPC and GQX; Administrative support: GQX; To provide research data or patients: YPC and GQX; Data collection and compilation: YPC; Data analysis and interpretation: YPC and YH; Manuscript writing: YPC; Final review of the draft: all authors. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study, approved by the Ethics Review Committee of Qingdao University Hospital, facilitated the retrieval of electronic medical records and laboratory data. The research was carried out adhering strictly to relevant rules and guidelines, with all participants and/or their legal guardians providing their informed consent (Ethics Registration Number: QYFYWLL27296). The research is performed in accordance with the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (81770699), the People's Livelihood Science and Technology Program of Qingdao, China (15-9-2-90-nsh).

Conflict of Interest

The authors declare no conflict of interest.

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