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Clinical characteristics, prognosis, and risk prediction model for adverse outcomes in patients suspected of coronary artery diseases and no significant stenosis on angiography

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Clinical characteristics, prognosis, and risk prediction model for adverse 1 2 outcomes in patients suspected of coronary artery diseases and no significant stenosis on angiography 3 4 Authors: Lei Zhu¹, Zheng-Kai Xue¹, Xue Wu², Jing-Kun Zhang³, Su-Tao Hu¹, Yu-Kun Zhang¹, 5 Tian-Shu Gu¹, Tong Liu¹, Seung-Woon Rha⁴, Kang-Yin Chen^{1*} 6 Affiliations: ¹ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, 7 Department of Cardiology, Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical 8 University, Tianjin, China. ² Institute for Global Health Sciences, University of California, San Francisco, CA, USA 9 ³ Cardiovascular Research Institute, University of California San Francisco, CA, USA 0 1 ⁴ Cardiovascular Center, Korea University Guro Hospital, Seoul, Republic of Korea. *Corresponding author: Kang-Yin Chen, MD, PhD, Tianjin Key Laboratory of Ionic-Molecular 2 3 Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, the 4 Second Hospital of Tianjin Medical University, No. 23, Pingjiang Road, Hexi District, Tianjin 300211, 5 China (chenkangyin@vip.126.com) 6 Word count: 2939

Abstract

Background and objectives

Although patients with suspected coronary artery disease and no significant stenosis on angiography are thought to have a better prognosis, some still experience adverse outcomes. This study aims to develop a predictive model for these adverse outcomes.

Methods

We retrospectively enrolled patients diagnosed with angina with nonobstructive coronary arteries (ANOCA) between January 2019 and June 2023, collecting relevant clinical data. We employed LASSO regression to select adverse prognostic risk factors, which were then integrated into a Cox proportional hazards regression model. Subsequently, we created a nomogram. Model performance was assessed for discrimination and calibration using the areas under the curve (AUC) and calibration plots, along with internal validation. The nomogram was utilized to categorize patients into high- and low-risk groups, and we compared their survival differences using the log-rank test.

Results

4,452 patients were included in the training cohort, and 1,482 in the testing cohort. The nomogram incorporated eight variables: age, hemoglobin, serum urea, serum sodium, ALT/AST ratio, NTproBNP, left atrial diameter, and LVEF. It showed good predictive performance for 1-year, 2-year, and 3-year event-free survival probabilities in both the training cohorts (AUC 0.82, 0.90, and 0.89) 60 35 and testing cohorts (AUC 0.75, 0.77, and 0.78). Calibration plots revealed close alignment between

predicted and actual event-free survival probabilities in both cohorts. Significant survival differences were observed among risk groups (log-rank p < 0.0001).

Conclusions

This study has successfully established a predictive model for adverse outcomes in ANOCA patients using clinically accessible variables, which could serve as a valuable tool to risk-stratify patients and customize their management and treatment strategies.

Key word

angina, coronary artery disease, MINOCA, prognosis, nomogram.

Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography, and coronary angiography, are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary 60 54 arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA) have been observed to experience more adverse outcomes compared to the general population[15–17]. Identifying highrisk patients remains a challenge.

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There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including highsensitivity troponin and lower HDL-C levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. To date, comprehensive studies that screen noninvasive indicators and develop a prognostic model are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study[19–21],

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which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the ASCVD score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance [22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

cuti This is a retrospective cohort study that consecutively enrolled patients who presented with suspected symptoms of CAD and underwent coronary angiography at the Department of Cardiology or Emergency Department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023. The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD statement [23].

Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of \geq 50% in a major epicardial coronary artery); (2) patients with a prior diagnosis of CAD, history of percutaneous coronary

intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or
kidney dysfunction, malignancies, or other conditions significantly affecting life expectancy; (4) those
with substantial missing baseline data; and (5) patients lost to follow-up. This study received approval
from the Ethics Committee of the Second Hospital of Tianjin Medical University, and the requirement
for written informed consent from patients was waived.

Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary angiography findings and other relevant details.

Follow-Up and Endpoints

Trained follow-up team members conducted regular patient follow-up after discharge at 30 days, 3
months, 6 months, and annually thereafter. Follow-up was performed using the hospital information
system, telephone, or email. The follow-up data for this study were collected up to August 1, 2023.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or coronary-artery bypass grafting (CABG) during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat 4 115 PCI, and CABG during follow-up.

Statistical Analysis

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15¹¹⁸ For the small amount of missing data in smoking and alcohol consumption history, multiple imputation was performed using the MICE package (Multiple Imputation by Chained Equations package). To establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate ²⁵₂₆122 the predictive model, while the validation set was utilized for model internal validation.

Categorical variables were described as frequencies and percentages, with group differences assessed 34¹²⁵ using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as ³⁶126 either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons were conducted using the t test or Kruskal-Wallis test as appropriate. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression model, and a 45 129 nomogram was generated based on the Cox regression analysis model. The discriminative ability of the predictive model was evaluated using AUC. The model's calibration was assessed through the calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility ₅₃132 of the nomogram.

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The total score for each patient was calculated based on the nomogram, and the study population was

stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. Event-free survival for the high- and low-risk groups in the training and validation sets was estimated by Kaplan-Meier method and compared with the log-rank test. All statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical Computing). All statistical tests were two- tailed, with a significance level set at P<0.05. Result Study Population and Patient Characteristics Out of a consecutive cohort of 17,816 patients who underwent coronary angiography for suspected coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients with a documented history of coronary heart disease were excluded. An additional 131 individuals were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative coronary angiography results (Figure 1). The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median follow-up time was 631 [270, 972] days. Detailed baseline data are provided in Supplementary Table 1. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

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Kaplan-Meier method was employed to estimate the survival without various adverse events for the total study population (**Supplementary Figure 1**).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (Supplementary Table 1). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (Figure 2A). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (Figure 2B). These variables were incorporated into a Cox proportional hazards regression model, with results presented in Table 2. A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(Figure 3). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

Table 2. Prediction of event-free survival probability using the Cox proportional hazards

regression model based on LASSO regression.

Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	<0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	<0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	<0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	<0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase;

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LVEF, left ventricular ejection fraction.

Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75, 0.77, and 0.78, respectively (figure 4).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-

degree line, indicating that predicted survival closely matches observed survival and demonstrating 4 190 good model calibration.

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Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in Figure 6, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

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Risk stratification

39²⁰¹ Considering that the study population consists of low-risk patients with non-obstructive coronary ⁴¹202 artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized 50²⁰⁵ as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves ⁵²206 depicting event-free survival were created for the two risk groups in the training and validation sets (Figure 7). Furthermore, MACE-event free survival of these groups is shown in Supplementary 58²⁰⁸ Figure 2. These results consistently demonstrated the model's efficacy in patient risk stratification.

Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic infomation, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [24]. However, research has

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consistently shown that following diagnostic assessments like coronary angiography, approximately 50% of patients do not exhibit obstructive coronary artery stenosis [5,16,25,26]. Traditionally, such patients were often considered to have a favorable prognosis and no significant cardiac conditions , potentially resulting in the omission of further diagnostic measures and therapeutic interventions [27– 29]. However, recent research has indicated that these patients face a significantly elevated risk of adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among female ANOCA patients [21,30,31]. Other studies have also demonstrated that ANOCA patients, regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to the general population[16,26,32].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [26]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations.

49 While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various underlying causes, such as coronary microvascular dysfunction (CMD), microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,33], emphasizing the critical importance of identifying high-risk ANOCA patients to optimize their further management. Current research on factors related to adverse outcomes in the ANOCA population is limited. One study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study solely relied solely on pretest clinical data and accessed coronary arteries through coronary CTA [18]. In contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [22,34]. Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinasetype plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

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studies conducted comprehensive screening of clinical variables or developed a predictive model. After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [35]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [36,37]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [38]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [39,40]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [41-44]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [45]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [46-49].

Our predictive model also considered echocardiographic parameters. Echocardiography is a
 noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive
 insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included.

Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [50-53]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [54,55].

Strengths and limitations

This study has several limitations. First, it is a retrospective study conducted at a single medical center, which may introduce some potential biases. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, due to the limitations of retrospective research, we were unable to further subdivide nonobstructive coronary stenosis into "normal coronary" (without significant coronary atherosclerosis) and "nonobstructive CAD" (stenosis <50%), although these two groups may have similar subsequent management. Finally, the predictive model lacks validation in an external population, but internal validation was performed, and it demonstrated good discrimination and calibration.

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Conclusion

In summary, we conducted a comprehensive evaluation of clinically accessible variables and

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3 4 312 5	successfully developed a predictive model for assessing adverse outcomes in patients with suspected
6 7 313 8	CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips clinicians with
9 10 ³¹⁴ 11	a valuable tool for risk stratification in ANOCA patients, allowing for optimized management and
12 ₃₁₅ 13 14	treatment strategies aimed at improving patient outcomes.
15316 16 17 18317	
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21 22 ³ 18 23	List of abbreviations
24 25 ₃₁₉ 26 27	ANOCA, angina with nonobstructive coronary arteries
28320 29	ACU, areas under the curve
30 31321 32	ALT, alanine transaminase
³³ 322 34 35	AST, aspartate transaminase
36323 37 38	LVEF, left ventricular ejection fraction
39324 40	CAD, coronary artery disease
42 ³²⁵ 43	MI, myocardial infarction
44326 45 46	CAG, coronary angiography
47327 48 49	CCTA, coronary computed tomography angiography
50 ³²⁸ 51	HDL-C, high-density lipoprotein cholesterol
52329 53 54	PCI, percutaneous coronary intervention
55330 56 57	CABG, coronary-artery bypass grafting
58331 59 60	MACE, major adverse cardiovascular events

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	Hoorweg BB, Willemsen RT, Cleef LE, <i>et al.</i> Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. <i>Heart Br Card Soc.</i> 2017;103:1727–32. doi: 10.1136/heartjnl-2016-310905
	Tsao CW, Aday AW, Almarzooq ZI, <i>et al.</i> Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. <i>Circulation</i> . 2022;145:e153–639. doi: 10.1161/CIR.00000000001052
	Virani SS, Newby LK, Arnold SV, <i>et al.</i> 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. <i>Circulation.</i> 2023;148:e9–119. doi: 10.1161/CIR.00000000001168
	Fihn SD, Gardin JM, Abrams J, <i>et al.</i> 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart

1 ว		
2 3 276		
4 3/6		Association Task Force on Practice Guidelines, and the American College of Physicians, American
5 377		Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for
6 378 7		Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation.
⁷ 379		2012;126:3097-137. doi: 10.1161/CIR.0b013e3182776f83
9		
10380	5	Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N
¹¹ 381		Engl J Med. 2010;362:886–95. doi: 10.1056/NEJMoa0907272
12		
14382	6	Rahman H, Corcoran D, Aetesam-Ur-Rahman M, et al. Diagnosis of patients with angina and non-
15383		obstructive coronary disease in the catheter laboratory. Heart Br Card Soc. 2019;105:1536-42.
¹⁶ 384		doi: 10.1136/heartjnl-2019-315042
17 18		
19385	7	Samuels BA, Shah SM, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 1-
20386		Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. J Am Coll Cardiol.
$^{21}_{22}387$		2023;82:1245–63. doi: 10.1016/j.jacc.2023.06.043
22		
24388	8	Shaw LJ, Merz CNB, Pepine CJ, et al. The economic burden of angina in women with suspected
25389		ischemic heart disease: results from the National Institutes of HealthNational Heart, Lung, and
$^{26}_{27}390$		Blood Institutesponsored Women's Ischemia Syndrome Evaluation. Circulation. 2006;114:894–
27		904. doi: 10.1161/CIRCULATIONAHA.105.609990
29		
30392	9	Gulati M, Khan N, George M, et al. Ischemia with no obstructive coronary artery disease (INOCA):
$^{31}_{22}393$		A patient self-report quality of life survey from INOCA international. Int J Cardiol. 2023;371:28–
32 33394		39. doi: 10.1016/i.jicard.2022.09.047
34		
35395	10	Takahashi T, Samuels BA, Li W, et al. Safety of Provocative Testing With Intracoronary
$^{36}_{37}396$		Acetylcholine and Implications for Standard Protocols. J Am Coll Cardiol. 2022;79:2367–78. doi:
38397		10.1016/j.jacc.2022.03.385
39		
⁴⁰ 398	11	Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for
41 42 ³⁹⁹		coronary artery disease. N Engl J Med. 2015;372:1291–300. doi: 10.1056/NEJMoa1415516
43		
44400	12	Udelson JE, Kelsey MD, Nanna MG, et al. Deferred Testing in Stable Outpatients With Suspected
⁴⁵ 401		Coronary Artery Disease: A Prespecified Secondary Analysis of the PRECISE Randomized
46 47402		Clinical Trial. JAMA Cardiol. Published Online First: 23 August 2023. doi:
48403		10.1001/jamacardio.2023.2614
49		
⁵⁰ 404	13	Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR
5 ₂ 405		Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of
53406		Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.
$^{54}_{-407}$		<i>Circulation</i> 2021.144.e368–454 doi: 10.1161/CIR.000000000000000000
55		
57408	14	Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of
58409		chronic coronary syndromes. Eur Heart J. 2020;41:407–77. doi: 10.1093/eurheartj/ehz425
59 60		
60		

1

2 3 410 15 Jordan KP, Timmis A, Croft P, et al. Prognosis of undiagnosed chest pain: linked electronic health 4 5 411 record cohort study. BMJ. 2017;357:j1194. doi: 10.1136/bmj.j1194 6 7 412 16 Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive 8 413 coronary artery disease is associated with increased risks of major adverse cardiovascular events. 9 10414 Eur Heart J. 2012;33:734-44. doi: 10.1093/eurheartj/ehr331 11 12415 17 Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women 13 14416 with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med. 2009;169:843-15417 16418 50. doi: 10.1001/archinternmed.2009.50 17 18 19419 18 Fordyce CB, Douglas PS, Roberts RS, et al. Identification of Patients With Stable Chest Pain 20420 Deriving Minimal Value From Noninvasive Testing: The PROMISE Minimal-Risk Tool, A ²¹421 22 Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiol. 2017;2:400-8. doi: 23422 10.1001/jamacardio.2016.5501 24 25423 19 Al-Badri A, Tahhan AS, Sabbak N, et al. Soluble Urokinase-Type Plasminogen Activator ²⁶424 27 Receptor and High-Sensitivity Troponin Levels Predict Outcomes in Nonobstructive Coronary 28425 Artery Disease. J Am Heart Assoc. 2020;9:e015515. doi: 10.1161/JAHA.119.015515 29 30426 20 Mansour M, Radaideh Q, Alaiwah MN, et al. Major adverse cardiac events in symptomatic women ³¹ 32</sub>427 with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART. 33428 Int J Cardiovasc Imaging. 2022;38:683–93. doi: 10.1007/s10554-021-02429-3 34 35429 21 Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and ³⁶ 37</sub>430 symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, 38431 Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) ³⁹432 angiographic core laboratory. Am Heart J. 2013;166:134-41. doi: 10.1016/j.ahj.2013.04.002 40 41 42⁴³³ 22 Sedlak T, Herscovici R, Cook-Wiens G, et al. Predicted Versus Observed Major Adverse Cardiac 43434 Event Risk in Women With Evidence of Ischemia and No Obstructive Coronary Artery Disease: ⁴⁴435 45 46436 A Report From WISE (Women's Ischemia Syndrome Evaluation). J Am Heart Assoc. 2020;9:e013234. doi: 10.1161/JAHA.119.013234 47 23 Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction 48437 ⁴⁹438 50 model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 51439 2015;350:g7594. doi: 10.1136/bmj.g7594 52 53440 24 Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for 54 55⁴41 coronary artery disease. N Engl J Med. 2015;372:1291-300. doi: 10.1056/NEJMoa1415516 56 57442 25 Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and No Obstructive Coronary Artery 58443 Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next 59 60⁴⁴⁴ Decade. Circulation. 2017;135:1075-92. doi: 10.1161/CIRCULATIONAHA.116.024534 20 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 23 of 45

1 2		
³ 445	26	Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and
4 5 446 6		risk of myocardial infarction. JAMA. 2014;312:1754-63. doi: 10.1001/jama.2014.14681
7 447	27	Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy.
⁸ 448		JAMA. 2005;293:477-84. doi: 10.1001/jama.293.4.477
10 11449	28	Lichtlen PR. Bargheer K. Wenzlaff P. Long-term prognosis of patients with anginalike chest pain
12450		and normal coronary angiographic findings <i>J Am Coll Cardiol</i> 1995:25:1013–8 doi:
¹³		10 1016/0735-1097(94)00519-v
14 ' ' '		
16452	29	Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left
¹⁷ 453		ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995;25:807-14. doi:
18 19 ⁴⁵⁴		10.1016/0735-1097(94)00507-M
20	20	Sharaf PL Daning CL Karanglay PA at al Datailed angiagraphic analysis of woman with
21455	30	sharar BL, Fepine CJ, Kelensky KA, <i>et al.</i> Detailed angiographic analysis of women with
23		Suspected Ischemic clest pain (pilot phase data from the NHLBI-sponsored women's Ischemia
24457		Syndrome Evaluation [wiSE] Study Angiographic Core Laboratory). Am J Caratol. 2001;87:937–
25458 26 27		41; A3. doi: 10.1016/s0002-9149(01)01424-2
²⁷ 459 28	31	Kenkre TS, Malhotra P, Johnson BD, et al. Ten-Year Mortality in the WISE Study (Women's
29460		Ischemia Syndrome Evaluation). Circ Cardiovasc Qual Outcomes. 2017;10:e003863. doi:
30461 31		10.1161/CIRCOUTCOMES.116.003863
³² ₃₃ 462	32	Sedlak TL, Lee M, Izadnegahdar M, et al. Sex differences in clinical outcomes in patients with
34463		stable angina and no obstructive coronary artery disease. Am Heart J. 2013;166:38-44. doi:
³⁵ 464 36		10.1016/j.ahj.2013.03.015
³⁷ 20465	33	Smilowitz NR, Prasad M, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 2-
39466		Program Development, Treatment, and Research Initiatives: JACC State-of-the-Art Review. J Am
⁴⁰ 467 41		Coll Cardiol. 2023;82:1264–79. doi: 10.1016/j.jacc.2023.06.044
42	34	Moreau P. d'Uscio I.V. Lüscher TF. Structure and reactivity of small arteries in aging <i>Cardiovasc</i>
43700	54	R_{as} 1008:37:247 53 doi: 10.1016/s0008.6363(07)00225.3
44409		Res. 1998,57.247–55. doi: 10.1010/s0008-0505(97)00225-5
⁴⁶ 470	35	Rymer IA Rao SV Anemia and coronary artery disease: pathophysiology prognosis and
47	20	treatment Coron Artery Dis 2018:29:161–7 doi: 10.1097/MCA.00000000000598
40 7 49		
50472	36	Gan T, Hu J, Liu W, et al. Causal Association Between Anemia and Cardiovascular Disease: A 2-
$^{51}_{52}473$		Sample Bidirectional Mendelian Randomization Study. J Am Heart Assoc. 2023;12:e029689. doi:
52 53474		10.1161/JAHA.123.029689
54		
55475	37	Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated
56 57 476		with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure.
58477		Circulation. 2003;107:223-5. doi: 10.1161/01.cir.0000052622.51963.fc
59		

⁶⁰478 38 Herzog CA, Asinger RW, Berger AK, *et al.* Cardiovascular disease in chronic kidney disease. A

³ 479 clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* ⁵ 480 2011;80:572–86. doi: 10.1038/ki.2011.223

1 2

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- ⁷ 481
 ⁸ 482
 ⁹ 482
 ⁹ 482
 ¹⁰⁴⁸³
 ⁹ 2022;22:50. doi: 10.1186/s12902-022-00954-3
- 40 Kirtane AJ, Leder DM, Waikar SS, *et al.* Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol.* 2005;45:1781–6. doi: 10.1016/j.jacc.2005.02.068
- ¹⁷487
 ¹⁸
 ¹⁹488
 ¹⁹488
 ¹⁹488
 ¹⁹488
 ¹⁰1016/j.cjca.2018.03.013
 ¹¹487
 <
- 42 Wannamethee SG, Shaper AG, Lennon L, *et al.* Mild hyponatremia, hypernatremia and incident cardiovascular disease and mortality in older men: A population-based cohort study. *Nutr Metab* 25492 *Cardiovasc Dis NMCD.* 2016;26:12–9. doi: 10.1016/j.numecd.2015.07.008
- 43 Ahn SY, Park YS, Lee SW, *et al.* Association Between Small Decrease in Serum Sodium Concentration within the Normal Range and All-Cause and Cardiovascular Mortality in Elderly Adults over 5 Years. *J Am Geriatr Soc.* 2016;64:510–7. doi: 10.1111/jgs.13937
- 44 Sajadieh A, Binici Z, Mouridsen MR, *et al.* Mild hyponatremia carries a poor prognosis in community subjects. *Am J Med.* 2009;122:679–86. doi: 10.1016/j.amjmed.2008.11.033
- ³⁶498
 ³⁷₃₈499
 ³⁶ardiac events in patients with heart failure: systematic review. *BMJ*. 2005;330:625. doi: 10.1136/bmj.330.7492.625
- 46 McKie PM, Rodeheffer RJ, Cataliotti A, *et al.* Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of heart failure. *Hypertens Dallas Tex 1979.* 2006;47:874–80. doi: 10.1161/01.HYP.0000216794.24161.8c
- 47 48505
 47 Wang TJ, Larson MG, Levy D, *et al.* Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* 2004;350:655–63. doi: 10.1056/NEJMoa031994 50
- ⁵¹507
 48 Rosenberg J, Schou M, Gustafsson F, *et al.* Prognostic threshold levels of NT-proBNP testing in primary care. *Eur Heart J.* 2009;30:66–73. doi: 10.1093/eurheartj/ehn525
- 49 Kistorp C, Raymond I, Pedersen F, *et al.* N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293:1609–16. doi: 10.1001/jama.293.13.1609
- ⁶⁰512 50 Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 2 3 513 Clinical Significance. JACC Cardiovasc Imaging. 2017;10:65-77. doi: 4 514 10.1016/j.jcmg.2016.11.003 5 6 7 515 51 Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk 8 516 factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995;98:476-84. doi: 9 10517 10.1016/S0002-9343(99)80348-9 11 12518 52 Marsan NA, Maffessanti F, Tamborini G, et al. Left atrial reverse remodeling and functional 13 14⁵¹⁹ improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-15520 dimensional echocardiography study. Am Heart J. 2011;161:314-21. doi: ¹⁶521 10.1016/j.ahj.2010.10.029 17 18 19522 53 Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the 20523 Framingham Circulation. 2004;110:1042-6. Heart Study. doi: ²¹524 10.1161/01.CIR.0000140263.20897.42 23 24525 54 Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a 25526 report of the Heart Failure Society of America, Heart Failure Association of the European Society ²⁶527 of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition 28528 of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of 29529 India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur ³⁰ 31⁵³⁰ J Heart Fail. 2021;23:352-80. doi: 10.1002/ejhf.2115 32 33531 55 Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the 34532 Management of Heart Failure: A Report of the American College of Cardiology/American Heart 35 36⁵³³ Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895–1032. doi: 10.1161/CIR.0000000000001063 37534 38 39 40535 41 42 43 Figure and table 44536 45 46 47 48⁵³⁷ Figure 1. Flowchart of study participation. CAD, coronary artery disease. 49 50 51 52 53 54 55 56





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Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit. The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray line represents the net benefit of not treating any patients. The curve in the middle represents the nomogram.



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Sm	nnlementary Figure 7 Kanlan-Meier curves for 1-year 2-year and 3-year MACF from
Suj	pplementary Figure 2. Kaplan-Meler curves for 1-year, 2-year, and 5-year MACE-free
sur	vival in the low-risk and high-risk groups in the training set (A) and validation set (B).

Consecutive patients underwent coronary angiography (n = 17816)







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Supplementary Table 1. Clinical data of the total population, training set and validation set.

Variable	Total	Train set	Validation set	p value
	N=5934	N=4452	N=1482	
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798
WBC, 10 ⁹ /L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831
Serum creatinine, µmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748
Uric acid, µmol/L	335 (100)	335 (101)	335 (99.0)	0.889
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844

Variable	Total	Train set	Validation set	p value
	N=5934	N=4452	N=1482	
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157
Total bilirubin, μmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257
Indirect Bilirubin, µmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242
Direct Bilirubin, µmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529
D-Dimer, µg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373	
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737	
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623	
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486	
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512	
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816	
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189	
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156	
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611	
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523	

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.







Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study Authors: Lei Zhu¹, Zheng-Kai Xue¹, Xue Wu², Jing-Kun Zhang³, Su-Tao Hu¹, Yu-Kun Zhang¹, Tian-Shu Gu¹, Tong Liu¹, Seung-Woon Rha⁴, Kang-Yin Chen^{1*} Affiliations: ¹ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical University, Tianjin, China ² Institute for Global Health Sciences, University of California, San Francisco, CA, USA ³ Cardiovascular Research Institute, University of California San Francisco, CA, USA ⁴ Cardiovascular Center, Korea University Guro Hospital, Seoul, Republic of Korea. *Corresponding author: Kang-Yin Chen, MD, PhD, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, the Second Hospital of Tianjin Medical University, No. 23, Pingjiang Road, Hexi District, Tianjin 300211, China (chenkangyin@vip.126.com) Word count: 3074

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7 Abstract

1

Objectives

To develop and validate a risk prediction model for adverse outcomes in patients with angina with

nonobstructive coronary arteries (ANOCA) confirmed by invasive coronary angiography.

Design

Retrospective cohort study.

23 Setting

4 A tertiary cardiovascular care center in East Asia.

25 Participants

From 17,816 consecutive patients undergoing coronary angiography for suspected coronary artery disease, 5,934 met ANOCA criteria after rigorous exclusion: (1) significant stenosis (≥50% luminal narrowing), (2) established coronary artery disease history, (3) incomplete baseline/follow-up data, (4) non-cardiovascular life-limiting conditions.

30 primary and secondary outcome measures

1 The primary outcome was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or 2 coronary-artery bypass grafting (CABG). The secondary outcome was major adverse cardiovascular 3 events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG.

Results

5 The derivation cohort (n=4,452) and validation cohort (n=1,482) demonstrated comparable baseline

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characteristics. The nomogram incorporated eight prognosticators: age, hemoglobin, serum urea, serum sodium, ALT/AST ratio, NT-proBNP, left atrial diameter, and LVEF. The prediction model showed robust discrimination for primary endpoint (derivation AUC: 0.82 [1-year], 0.90 [2-year], 0.89 [3-year]; validation AUC: 0.75, 0.77, 0.78). Calibration plots revealed close alignment between predicted and actual event-free survival probabilities in both cohorts. Risk stratification identified two distinct prognostic groups with significant survival differences (log-rank p < 0.0001). Conclusions This predictive model integrates routinely available clinical parameters to accurately stratify mortality and cardiovascular risk in ANOCA patients, providing a potential valuable decision-support tool for . N.C. personalized therapeutic strategies. Strengths and limitations of this study This study utilized a large sample size (n=5934) with rigorous internal validation through training and testing cohorts. Leveraged LASSO-penalized Cox regression with 10-fold cross-validation to optimize model generalizability. The nomogram integrates routinely available clinical variables, enhancing clinical applicability. Limitations include the retrospective design, which may introduce selection bias. Data were derived from a single center, potentially limiting generalizability.

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60 Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography, and coronary angiography, are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA) have been observed to experience more adverse outcomes compared to the general population [15-17]. Identifying high-risk individuals in ANOCA patients remains a challenge.

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There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including highsensitivity troponin and lower HDL-C levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. To date, comprehensive studies that screen noninvasive indicators and develop a prognostic model are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study[19–21], which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the ASCVD score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance[22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

0 This is a retrospective cohort study that consecutively enrolled patients who presented with suspected

symptoms of CAD and underwent coronary angiography at the Department of Cardiology or Emergency Department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023. The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD statement [23].

ANOCA patients were defined as angina with nonobstructive epicardial coronary arteries (stenosis <50%), adhering to current expert consensus[7]. Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of \geq 50% in a major epicardial coronary artery[7,24]); (2) patients with a prior diagnosis of CAD, history of percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or kidney dysfunction, malignancies, or other noncardiovascular conditions significantly affecting life expectancy; (4) those with substantial missing baseline data; and (5) patients lost to follow-up. This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, with a waiver for written informed consent granted for the retrospective use of fully anonymized clinical data (No. KY2025K008). Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

18 Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic
 information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary

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1 angiography findings and other relevant details.

23 Follow-Up and Endpoints

A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and Z.K.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria[25,26]. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or coronary-artery bypass grafting (CABG) during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG during follow-up. The composite endpoint was selected based on its established utility in prognostic studies of ANOCA [22,27–29]. **Statistical Analysis**

142	For the small amount of missing data in smoking and alcohol consumption history, multiple imputation
143	was performed using the MICE package (Multiple Imputation by Chained Equations package). To
144	establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training
9 145	set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate
3 9146)	the predictive model, while the validation set was utilized for model internal validation.
147	
148	Categorical variables were described as frequencies and percentages, with group differences assessed
5 7149 8	using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as
) 150	either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons
151	were conducted using the t test or Kruskal–Wallis test as appropriate. Variables with VIF \geq 5 were
152	excluded prior to LASSO regression to mitigate multicollinearity. The variables selected through
, 3153)	LASSO regression were incorporated into the Cox proportional hazards regression model, and a
154	nomogram was generated based on the Cox regression analysis model. The discriminative ability of
155	the predictive model was evaluated using AUC. The model's calibration was assessed through the
5 5156 7	calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility
3 157	of the nomogram.
158	

The total score for each patient was calculated based on the nomogram, and the study population was stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. Event-free survival for the high- and low-risk groups in the training

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4 162 5	and validation sets was estimated by Kaplan-Meier method and compared with the log-rank test. All
6 7 163 8	statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical
9 10 ¹⁶⁴ 11	Computing). All statistical tests were two- tailed, with a significance level set at P<0.05.
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15166 16	Patient and public involvement
17 18 ¹⁶⁷	None.
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31 32171	Out of a consecutive cohort of 17.816 natients who underwent coronary angiography for suspected
33	out of a consecutive conort of 17,010 patients who anderwent coronary anglography for suspected
34 35172 36	coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients
³⁷ 173 38	with a documented history of coronary heart disease were excluded. An additional 131 individuals
40174 41	were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such
42 43175 44	as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative
45 46176	coronary angiography results (Figure 1).
47 48177 49	
50 51178 52	The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median
53 54179 55	follow-up time was 631 [270, 972] days. Detailed baseline data are provided in Supplementary Table
⁵⁶ 180	1. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had
59181 60	MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

Kaplan-Meier method was employed to estimate the survival without various adverse events for the
total study population (Supplementary Figure 1).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (Supplementary Table 1). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (Figure 2A). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (Figure 2B). These variables were incorporated into a Cox proportional hazards regression model, with results presented in Table 1. All models satisfied proportional hazards assumptions (global test p=0.057). A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(Figure 3). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

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Table 1. Prediction of event-free survival probability using the Cox proportional hazards

regression	model	based	on	LASSO	regression.
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Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	< 0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	< 0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	< 0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	< 0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase;

LVEF, left ventricular ejection fraction.

Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75,

0.77, and 0.78, respectively (figure 4).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the

training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-

degree line, indicating that predicted survival closely matches observed survival and demonstrating

good model calibration.

Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in Figure 6, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

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Risk stratification

Considering that the study population consists of low-risk patients with non-obstructive coronary artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves depicting event-free survival were created for the two risk groups in the training and validation sets (Figure 7). Furthermore, MACE-event free survival of these groups is shown in Supplementary Figure 2. These results consistently demonstrated the model's efficacy in patient risk stratification.

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Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic information, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [30]. However, research has

56	consistently shown that following diagnostic assessments like coronary angiography, approximately
57	50% of patients do not exhibit obstructive coronary artery stenosis [5,16,24,31]. Traditionally, such
58	patients were often considered to have a favorable prognosis and no significant cardiac conditions,
59	potentially resulting in the omission of further diagnostic measures and therapeutic interventions [32-
60	34]. However, recent research has indicated that these patients face a significantly elevated risk of
61	adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year
62	follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of
63	cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among
64	female ANOCA patients [21,35,36]. Other studies have also demonstrated that ANOCA patients,
65	regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to
66	the general population[16,31,37].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [31]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

276 While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

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with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various underlying causes, such as coronary microvascular dysfunction (CMD), microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,38], emphasizing the critical importance of identifying high-risk ANOCA patients to optimize their further management. Current research on factors related to adverse outcomes in the ANOCA population is limited. One study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study solely relied solely on pretest clinical data and accessed coronary arteries through coronary CTA [18]. In contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [39,40].

Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinasetype plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

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studies conducted comprehensive screening of clinical variables or developed a predictive model. 299 After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [41]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [42,43]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [44]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [45,46]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [47-50]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [51]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [52–55].

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53316 Our predictive model also considered echocardiographic parameters. Echocardiography is a 54 55 56³17 noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive 57 ⁵⁸318 59 insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included. 60

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Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [56-59]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [60,61].

Limitations

This study has several limitations. First, the retrospective design precludes control of treatment strategies and introduces potential selection bias. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, the inability to subclassify ANOCA patients into those with versus without atherosclerosis represents an important limitation, as pathophysiological differences between these cohorts may contribute to population heterogeneity. However, this aligns with current guideline definitions, and future studies incorporating intracoronary imaging could refine risk stratification. Finally, while the predictive model developed from single-center data has not yet undergone external validation, internal validation confirmed its robust discrimination and calibration, indicating strong performance within the original cohort.

Conclusion

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In summary, we conducted a comprehensive evaluation of clinically accessible variables and successfully developed a predictive model for assessing adverse outcomes in angina patients with suspected CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips clinicians with a valuable tool for risk stratification in ANOCA patients, allowing for optimized management and treatment strategies aimed at improving patient outcomes.

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6 List of abbreviations

ANOCA, angina with nonobstructive coronary arteries

ACU, areas under the curve

ALT, alanine transaminase

AST, aspartate transaminase

²351 LVEF, left ventricular ejection fraction

5352 CAD, coronary artery disease

MI, myocardial infarction

⁵⁰354 CAG, coronary angiography

53355 CCTA, coronary computed tomography angiography

56356 HDL-C, high-density lipoprotein cholesterol

PCI, percutaneous coronary intervention

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4 358 5	CABG, coronary-artery bypass grafting
6 7 359	MACE, major adverse cardiovascular events
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³⁷ 369	Data availability statement
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41370	The original data supporting the findings of this study can be obtained from the corresponding author
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Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.
2 3 399 Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline 3 4 5 400 for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart 6 401 Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. 7 402 Circulation. 2023;148:e9-119. doi: 10.1161/CIR.00000000001168 8 9 10403 4 Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline 11404 for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive 12 13⁴⁰⁵ Summary: A Report of the American College of Cardiology Foundation/American Heart 14406 Association Task Force on Practice Guidelines, and the American College of Physicians, American 15407 Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for 16 17⁴⁰⁸ Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 18409 2012;126:3097-137. doi: 10.1161/CIR.0b013e3182776f83 19 ²⁰410 Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N 5 21 Engl J Med. 2010;362:886-95. doi: 10.1056/NEJMoa0907272 23 24412 Rahman H, Corcoran D, Aetesam-Ur-Rahman M, et al. Diagnosis of patients with angina and non-6 ²⁵413 obstructive coronary disease in the catheter laboratory. Heart Br Card Soc. 2019;105:1536-42. 27414 doi: 10.1136/heartjnl-2019-315042 28 29415 Samuels BA, Shah SM, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 1-7 ³⁰ 31</sub>416 Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;82:1245-63. doi: 10.1016/j.jacc.2023.06.043 32417 33 34418 Shaw LJ, Merz CNB, Pepine CJ, et al. The economic burden of angina in women with suspected 8 35 36⁴¹⁹ ischemic heart disease: results from the National Institutes of Health--National Heart, Lung, and 37420 Blood Institute--sponsored Women's Ischemia Syndrome Evaluation. Circulation. 2006;114:894– ³⁸421 904. doi: 10.1161/CIRCULATIONAHA.105.609990 39 40 41422 9 Gulati M, Khan N, George M, et al. Ischemia with no obstructive coronary artery disease (INOCA): 42423 A patient self-report quality of life survey from INOCA international. Int J Cardiol. 2023;371:28-⁴³424 39. doi: 10.1016/j.ijcard.2022.09.047 44 45 .5 46⁴²⁵ 10 Takahashi T, Samuels BA, Li W, et al. Safety of Provocative Testing With Intracoronary 47426 Acetylcholine and Implications for Standard Protocols. J Am Coll Cardiol. 2022;79:2367-78. doi: 48 49</sub>427 10.1016/j.jacc.2022.03.385 50 51428 11 Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for 52429 coronary artery disease. N Engl J Med. 2015;372:1291-300. doi: 10.1056/NEJMoa1415516 53 ⁵⁴₅₅430 12 Udelson JE, Kelsey MD, Nanna MG, et al. Deferred Testing in Stable Outpatients With Suspected 56431 Coronary Artery Disease: A Prespecified Secondary Analysis of the PRECISE Randomized 57432 Clinical Trial. JAMA Cardiol. Published Online First: August 2023. doi: 23 58 59⁴33 10.1001/jamacardio.2023.2614 60

Page 25 of 42

1 2		
$3 \\ 4 \\ 5 \\ 435$	13	Gulati M, Levy PD, Mukherjee D, <i>et al.</i> 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of
6 436 7 437		Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. <i>Circulation</i> . 2021;144:e368–454. doi: 10.1161/CIR.000000000001029
9 10438 11439	14	Knuuti J, Wijns W, Saraste A, <i>et al.</i> 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. <i>Eur Heart J.</i> 2020;41:407–77. doi: 10.1093/eurheartj/ehz425
12 13 14 ⁴⁴⁰ 15441 16	15	Jordan KP, Timmis A, Croft P, <i>et al.</i> Prognosis of undiagnosed chest pain: linked electronic health record cohort study. <i>BMJ</i> . 2017;357:j1194. doi: 10.1136/bmj.j1194
17 ₄₄₂ 18 19 ⁴⁴³ 20444 21	16	Jespersen L, Hvelplund A, Abildstrøm SZ, <i>et al.</i> Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. <i>Eur Heart J.</i> 2012;33:734–44. doi: 10.1093/eurheartj/ehr331
²² 445 23 24446 25447 26 448 27	17	Gulati M, Cooper-DeHoff RM, McClure C, <i>et al.</i> Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. <i>Arch Intern Med.</i> 2009;169:843–50. doi: 10.1001/archinternmed.2009.50
28 29449 30450 31 32451 33452 34	18	Fordyce CB, Douglas PS, Roberts RS, <i>et al.</i> Identification of Patients With Stable Chest Pain Deriving Minimal Value From Noninvasive Testing: The PROMISE Minimal-Risk Tool, A Secondary Analysis of a Randomized Clinical Trial. <i>JAMA Cardiol.</i> 2017;2:400–8. doi: 10.1001/jamacardio.2016.5501
³⁵ 453 ³⁶ ₃₇ 454 38455 39	19	Al-Badri A, Tahhan AS, Sabbak N, <i>et al.</i> Soluble Urokinase-Type Plasminogen Activator Receptor and High-Sensitivity Troponin Levels Predict Outcomes in Nonobstructive Coronary Artery Disease. <i>J Am Heart Assoc.</i> 2020;9:e015515. doi: 10.1161/JAHA.119.015515
⁴⁰ 456 41 42 ⁴⁵⁷ 43458 44	20	Mansour M, Radaideh Q, Alaiwah MN, <i>et al.</i> Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART. <i>Int J Cardiovasc Imaging.</i> 2022;38:683–93. doi: 10.1007/s10554-021-02429-3
45 ₄₅₉ 46 47460 48461 49 462 50	21	Sharaf B, Wood T, Shaw L, <i>et al.</i> Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. <i>Am Heart J.</i> 2013;166:134–41. doi: 10.1016/j.ahj.2013.04.002
51 52463 53464 54 55 56466 57	22	Sedlak T, Herscovici R, Cook-Wiens G, <i>et al.</i> Predicted versus observed major adverse cardiac event risk in women with evidence of ischemia and no obstructive coronary artery disease: A report from WISE (women's ischemia syndrome evaluation). <i>J Am Heart Assoc.</i> 2020;9:e013234. doi: 10.1161/JAHA.119.013234
58467 59 60 ⁴⁶⁸	23	Collins GS, Reitsma JB, Altman DG, <i>et al.</i> Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. <i>BMJ</i> .

6 470 7 471

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13 14 15⁴⁷⁵

2015;350:g7594. doi: 10.1136/bmj.g7594 24 Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017;135:1075-92. doi: 10.1161/CIRCULATIONAHA.116.024534 25 K T, Js A, As J, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018;72. doi: 10.1016/j.jacc.2018.08.1038 26 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/american 2019;50:e344-418. stroke association. Stroke. doi: 10.1161/STR.000000000000211 27 Mansour M, Radaideh Q, Alaiwah MN, et al. Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: Pooled analysis from PROMISE and SCOT-HEART. Int J Cardiovasc Imaging. 2022;38:683-93. doi: 10.1007/s10554-021-02429-3 28 Al-Badri A, Tahhan AS, Sabbak N, et al. Soluble urokinase-type plasminogen activator receptor and high-sensitivity troponin levels predict outcomes in nonobstructive coronary artery disease. J Am Heart Assoc. 2020;9:e015515. doi: 10.1161/JAHA.119.015515 29 Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: Results from the NIH-NHLBI-sponsored women's ischaemia syndrome evaluation (WISE) study. Eur Heart J. 2006;27:1408-15. doi: 10.1093/eurheartj/ehl040 30 Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372:1291-300. doi: 10.1056/NEJMoa1415516 31 Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA. 2014;312:1754-63. doi: 10.1001/jama.2014.14681 32 Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA. 2005;293:477-84. doi: 10.1001/jama.293.4.477 33 Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. J Am Coll Cardiol. 1995;25:1013-8. doi: 10.1016/0735-1097(94)00519-v 34 Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995;25:807-14. doi: 10.1016/0735-1097(94)00507-M 35 Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with

1		
² ³ 503		suspected ischemic chest pain (pilot phase data from the NHI BL-sponsored Women's Ischemia
4 ⁵⁰⁵		Suspected Iselemic cliest pair (plot plase data from the MILDI-sponsored women's Iselemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory) <i>Am I Cardiol</i> 2001:87:937–
5 504 6 505		41: A3 doi: 10 1016/s0002-9149(01)01424-2
7		+1, <i>NS</i> . doi: 10.1010/50002 91+9(01)01+2+ 2
$^{8}_{0}$ 506	36	Kenkre TS, Malhotra P, Johnson BD, et al. Ten-Year Mortality in the WISE Study (Women's
, 10507		Ischemia Syndrome Evaluation). Circ Cardiovasc Qual Outcomes. 2017;10:e003863. doi:
11508		10.1161/CIRCOUTCOMES.116.003863
12 13		
14509	37	Sedlak TL, Lee M, Izadnegahdar M, et al. Sex differences in clinical outcomes in patients with
15510		stable angina and no obstructive coronary artery disease. Am Heart J. 2013;166:38-44. doi:
¹⁶ 511 17		10.1016/j.ahj.2013.03.015
18 ₅₁₀	20	Swillswitz ND Dress I M Willswar DL of all Comments arises Management of ANOCA Det 2
19 ⁵¹²	38	Smilowitz NR, Prasad M, Widmer RJ, <i>et al.</i> Comprehensive Management of ANOCA, Part 2-
20513		<i>Coll Condition</i> 2022/82/12/14/70/doi: 10.101//j.jecc.2022.0/.044
22		Coll Caratol. 2023;82:1264–79. doi: 10.1016/j.jacc.2023.06.044
23 24515	39	Sedlak T Herscovici R Cook-Wiens G <i>et al.</i> Predicted Versus Observed Major Adverse Cardiac
25516	U y	Event Risk in Women With Evidence of Ischemia and No Obstructive Coronary Artery Disease
$^{26}517$		A Report From WISE (Women's Ischemia Syndrome Evaluation). J Am Heart Assoc.
27		2020 [.] 9 [.] e013234 doi [.] 10 1161/JAHA 119 013234
29		
30519	40	Moreau P, d'Uscio LV, Lüscher TF. Structure and reactivity of small arteries in aging. Cardiovasc
$\frac{31}{32}520$		Res. 1998;37:247-53. doi: 10.1016/s0008-6363(97)00225-3
33		
34521	41	Rymer JA, Rao SV. Anemia and coronary artery disease: pathophysiology, prognosis, and
35522 36		treatment. Coron Artery Dis. 2018;29:161–7. doi: 10.1097/MCA.0000000000000598
³⁷ 523	42	Gan T. Hu I. Liu W. et al. Causal Association Between Anemia and Cardiovascular Disease: A 2-
38 ⁵²⁵ 39524	12	Sample Bidirectional Mendelian Randomization Study <i>LAm Heart Assoc</i> 2023:12:e029689 doi:
⁴⁰ 525		10 1161/JAHA 123 029689
41		
42 43 ⁵²⁶	43	Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated
44527		with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure.
⁴⁵ 528		Circulation. 2003;107:223-5. doi: 10.1161/01.cir.0000052622.51963.fc
40		
48 ⁵²⁹	44	Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A
49530 50		clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int.
50531 51		2011;80:572–86. doi: 10.1038/ki.2011.223
52	15	Liu E. Ma G. Tong C. at al. Elevated blood uses nitrogen-to-creatining ratio increased the risk of
54533	Ъ	Coronary Artery Disease in patients living with type 2 diabetes mellitus <i>BMC Endocr Disord</i>
⁵⁵ 534		2022.22.50 doi: 10.1186/s12902_022_00954_3
56 ^{° ° ¬}		2022,22.30. uoi. 10.1100/312/02 022 00/34 5
58535	46	Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of
⁵⁹ 536		subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced
60		

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

glomerular filtration rates. J Am Coll Cardiol. 2005;45:1781-6. doi: 10.1016/j.jacc.2005.02.068

8.03.013
, Shaper AG, Lennon L, <i>et al</i> . Mild hyponatremia, hypernatremia and incident ease and mortality in older men: A population-based cohort study. <i>Nutr Metab</i> <i>MCD</i> . 2016;26:12–9. doi: 10.1016/j.numecd.2015.07.008
S, Lee SW, <i>et al.</i> Association Between Small Decrease in Serum Sodium hin the Normal Range and All-Cause and Cardiovascular Mortality in Elderly rs. <i>J Am Geriatr Soc.</i> 2016;64:510–7. doi: 10.1111/jgs.13937
ci Z, Mouridsen MR, <i>et al.</i> Mild hyponatremia carries a poor prognosis in tts. <i>Am J Med.</i> 2009;122:679–86. doi: 10.1016/j.amjmed.2008.11.033
E, Dobson A, <i>et al.</i> How well does B-type natriuretic peptide predict death and patients with heart failure: systematic review. <i>BMJ.</i> 2005;330:625. doi 7492.625
neffer RJ, Cataliotti A, <i>et al.</i> Amino-terminal pro-B-type natriuretic peptide and peptide: biomarkers for mortality in a large community-based cohort free of <i>Hypertens Dallas Tex 1979.</i> 2006;47:874–80. doi 0000216794.24161.8c
n MG, Levy D, <i>et al.</i> Plasma natriuretic peptide levels and the risk of ents and death. <i>N Engl J Med.</i> 2004;350:655–63. doi: 10.1056/NEJMoa031994
ou M, Gustafsson F, <i>et al.</i> Prognostic threshold levels of NT-proBNP testing in <i>Heart J.</i> 2009;30:66–73. doi: 10.1093/eurheartj/ehn525
ond I, Pedersen F, <i>et al.</i> N-terminal pro-brain natriuretic peptide, C-reactive ry albumin levels as predictors of mortality and cardiovascular events in older 05;293:1609–16. doi: 10.1001/jama.293.13.1609
yaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and ficance. <i>JACC Cardiovasc Imaging</i> . 2017;10:65–77. doi 16.11.003
reda J, Tate RB, <i>et al.</i> The natural history of atrial fibrillation: incidence, risk nosis in the Manitoba Follow-Up Study. <i>Am J Med.</i> 1995;98:476–84. doi 643(99)80348-9
fessanti F, Tamborini G, <i>et al.</i> Left atrial reverse remodeling and functional er mitral valve repair in degenerative mitral regurgitation: a real-time 3-
25

538 47 He X, Liu C, Chen Y, et al. Risk of Cardiovascular Mortality Associated With Serum Sodium and Cardiol 2018.34.999-1003 539 Chloride in the General Population Can I doi.

540 10.1016/j.cjca.201

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- 15 16544 49 Ahn SY, Park Y 1 17545 Concentration with 18 19546 Adults over 5 Yea
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24 25⁵⁴⁹ 51 Doust JA, Pietrzak ł 26550 cardiac events in ²⁷551 28 10.1136/bmj.330.7

- 29 30552 52 McKie PM, Rodeh ł f 31553 **B-type** natriuretic ³² 33⁵⁵⁴ heart failure. 34555 10.1161/01.HYP.0
- 36556 f 53 Wang TJ, Larson ³⁷ 38⁵⁵⁷ cardiovascular eve
- 39 40558 54 Rosenberg J, Scho 1 ⁴¹559 primary care. Eur 42
- 43 44560 55 Kistorp C, Raymo е 45561 protein, and urina 46 47 562 adults. JAMA. 200
- 48 49563 56 Thomas L, Abhay 1 50564 Clinical Signi : ⁵¹₅₂565 10.1016/j.jcmg.20
- 53 54566 57 Krahn AD, Manfr ζ 55567 factors, and progr ⁵⁶568 10.1016/S0002-93
- 58 59569 58 Marsan NA, Maf 1 60570 improvement afte

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3 571		dimonsional achoeserdiography study Am Hagert I 2011:161:214 21 doi:
4 572		unnensional echocardiography study. Am Heart J. $2011,101.514-21$. doi: 10.1016/j.eki.2010.10.020
5 372		10.1016/j.anj.2010.10.029
7 573	59	Lloyd-Iones DM Wang TI Leip EP <i>et al</i> Lifetime risk for development of atrial fibrillation: the
⁸ 574	09	Framingham Heart Study Circulation 2004:110:1042-6 doi:
9 577		10 1161/01 CIP 0000140263 20897 42
10575		10.1101/01.CIK.0000140203.20897.42
12576	60	Bozkurt B Coats AJS Tsutsui H <i>et al.</i> Universal definition and classification of heart failure: a
13		report of the Heart Failure Society of America. Heart Failure Association of the European Society
14°77		of Cardiology Japanese Heart Failure Society and Writing Committee of the Universal Definition
16579		of Heart Failure: Endorsed by the Canadian Heart Failure Society. Heart Failure Association of
17		India Cardiac Society of Australia and New Zealand and Chinese Heart Failure Association Eur
18500		<i>Heart Fail</i> 2021:23:352, 80, doi: 10.1002/eibf.2115
20		<i>5 Treart Patt.</i> 2021,25.552–60. doi: 10.1002/CJIII.2115
²¹ 582	61	Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the
22 23583		Management of Heart Failure: A Report of the American College of Cardiology/American Heart
24584		Association Joint Committee on Clinical Practice Guidelines. <i>Circulation</i> . 2022:145:e895–1032.
²⁵ 585		doi: 10.1161/CIR.0000000000000000
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Figure 4. Receiver operating characteristic curve for the 1-, 2-, and 3-year primary endpoints of the nomogram in the training set (A) and validation set (B). AUC, area under receiver operating characteristic curve. Figure 5. Calibration plot of predicted 1-, 2-, and 3-year event-free survival based on the **nomogram in the training set and validation set.** (A–C) Training set; (D–F) Validation set. Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit. The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray line represents the net benefit of not treating any patients. The curve in the middle represents the nomogram. Figure 7. Kaplan-Meier curves for primary endpoint event-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B). Supplementary Table 1. Clinical data of the total population, training set and validation set. Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population.

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3 4 619 5	Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-
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Supplementary Table 1. Clinical data of the total population, training set and validation set.

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499	
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563	
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698	
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909	
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094	
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820	
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595	
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185	
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993	
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340	
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757	
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798	
WBC, 10 ⁹ /L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969	
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881	
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831	
Serum creatinine, µmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748	
Uric acid, µmol/L	335 (100)	335 (101)	335 (99.0)	0.889	
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829	
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649	
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515	
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844	

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968	
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406	
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353	
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169	
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341	
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157	
Total bilirubin, µmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257	
Indirect Bilirubin, µmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242	
Direct Bilirubin, µmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611	
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820	
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919	
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485	
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083	
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498	
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627	
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536	
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415	
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529	
D-Dimer, µg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110	
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579	
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331	

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373	
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737	
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623	
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486	
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512	
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816	
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189	
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156	
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611	
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523	

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.



Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population

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Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).

Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study Authors: Lei Zhu¹, Zheng-Kai Xue¹, Xue Wu², Jing-Kun Zhang³, Su-Tao Hu¹, Yu-Kun Zhang¹, Tian-Shu Gu¹, Tong Liu¹, Seung-Woon Rha⁴, Kang-Yin Chen^{1*} Affiliations: ¹ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical University, Tianjin, China ² Institute for Global Health Sciences, University of California, San Francisco, CA, USA ³ Cardiovascular Research Institute, University of California San Francisco, CA, USA ⁴ Cardiovascular Center, Korea University Guro Hospital, Seoul, Republic of Korea. *Corresponding author: Kang-Yin Chen, MD, PhD, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, the Second Hospital of Tianjin Medical University, No. 23, Pingjiang Road, Hexi District, Tianjin 300211, China (chenkangyin@vip.126.com) Word count: 3081

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2 3 4 5 6	17	Abstract				
7 8 9 10	18	Objectives				
11 12 13 14 15 16	19	To develop and validate a risk prediction model for adverse outcomes in patients with angina with				
	20	nonobstructive coronary arteries (ANOCA) confirmed by invasive coronary angiography.				
17 17 18	21	Design				
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34	22	Retrospective cohort study.				
	23	Setting				
	24	A tertiary cardiovascular care center in China.				
	25	Participants				
	26	From 17,816 consecutive patients undergoing coronary angiography for suspected coronary artery				
	27	disease, 5,934 met ANOCA criteria after rigorous exclusion: (1) significant stenosis (≥50% luminal				
35 36 37	28	narrowing), (2) established coronary artery disease history, (3) incomplete baseline/follow-up data, (4)				
38 39 40	29	non-cardiovascular life-limiting conditions.				
41 42 43	30	primary and secondary outcome measures				
44 45	31	The primary outcome was a composite of all-cause death, nonfatal myocardial infarction (MI), stroke,				
46 47 48	32	and repeat percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG). The				
49 50	33	secondary outcome was major adverse cardiovascular events (MACE), defined as cardiac-related death				
52 53 54 55	34	nonfatal MI, nonfatal stroke, repeat PCI, and CABG.				
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death,

The derivation cohort (n=4,452) and validation cohort (n=1,482) demonstrated comparable baseline characteristics. The nomogram incorporated eight prognosticators: age, hemoglobin, serum urea, serum sodium, alanine aminotransferase (ALT) / aspartate aminotransferase (AST) ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left atrial diameter, and left ventricular ejection fraction (LVEF). The prediction model showed robust discrimination for primary endpoint, achieving area under the curve (AUC) values of 0.82 (1-year), 0.90 (2-year), and 0.89 (3-year) in the derivation cohort, with corresponding validation cohort AUCs of 0.75, 0.77, and 0.78. Calibration plots revealed close alignment between predicted and actual event-free survival probabilities in both cohorts. Risk stratification identified two distinct prognostic groups with significant survival differences (log-rank Lien p < 0.0001).

Conclusions

This predictive model integrates routinely available clinical parameters to accurately stratify mortality and cardiovascular risk in ANOCA patients, providing a potential valuable decision-support tool for personalized therapeutic strategies.

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Strengths and limitations of this study

- This study utilized a large sample size (n=5934) with rigorous internal validation through training and testing cohorts.
- Leveraged LASSO-penalized Cox regression with 10-fold cross-validation to optimize model

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3											
4 5	55	generalizability.									
6 7 8	56	• The nomogram integrates routinely available clinical variables, enhancing clinical applicability.									
9 10	57	• Limitations include the retrospective design, which may introduce selection bias.									
12 13	58	• Data were derived from a single center, potentially limiting generalizability.									
14 15	59										
16 17 18 19 20	60										
21	61	Key word									
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25 26	62	Angina, coronary artery disease, MINOCA, prognosis, nomogram.									
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Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography (CCTA), and coronary angiography (CAG), are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by CAG or CCTA have been observed to experience more adverse outcomes compared to the general population[15–17]. Identifying high-risk individuals in ANOCA patients remains a challenge.

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There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including highsensitivity troponin and lower high-density lipoprotein cholesterol (HDL-C) levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. comprehensive studies that screen noninvasive indicators and develop a prognostic model To date. are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study [19–21], which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the Atherosclerotic Cardiovascular Disease (ASCVD) score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance[22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

This is a retrospective cohort study that consecutively enrolled patients who presented with suspected

symptoms of CAD and underwent coronary angiography at the department of cardiology or emergency
department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023.
The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese
city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD
statement [23].

ANOCA patients were defined as angina with nonobstructive epicardial coronary arteries (stenosis <50%), adhering to current expert consensus[7]. Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of \geq 50% in a major epicardial coronary artery[7,24]); (2) patients with a prior ³¹115 diagnosis of CAD, history of percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or kidney dysfunction, malignancies, or other non-37¹¹⁷ cardiovascular conditions significantly affecting life expectancy; (4) those with substantial missing ³⁹118 baseline data; and (5) patients lost to follow-up. This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, with a waiver for written informed consent granted for the retrospective use of fully anonymized clinical data (No. KY2025K008).

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22 Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary

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angiography findings and other relevant details.

Follow-Up and Endpoints

A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and Z.K.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria[25,26]. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or CABG during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG during follow-up. The composite endpoint was selected based on its established utility in prognostic studies of ANOCA [22,27–29].

Statistical Analysis

For the small amount of missing data in smoking and alcohol consumption history, multiple imputation was performed using the MICE package (Multiple Imputation by Chained Equations package). To establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate the predictive model, while the validation set was utilized for model internal validation. Categorical variables were described as frequencies and percentages, with group differences assessed using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons were conducted using the t test or Kruskal–Wallis test as appropriate. Variables with variance inflation factor (VIF) \geq 5 were excluded prior to LASSO regression to mitigate multicollinearity. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression 41¹⁵⁸ model, and a nomogram was generated based on the Cox regression analysis model. The discriminative ability of the predictive model was evaluated using area under the curve (AUC). The model's calibration was assessed through the calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility of the nomogram. The total score for each patient was calculated based on the nomogram, and the study population was

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event-free survival probability. Event-free survival for the high- and low-risk groups in the training

4 166 and validation sets was estimated by Kaplan-Meier method and compared with the log-rank test. All statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical 10¹⁶⁸ Computing). All statistical tests were two- tailed, with a significance level set at P<0.05. Patient and public involvement 18¹⁷¹ None. ²⁰172 ²⁴173 Result **Study Population and Patient Characteristics** Out of a consecutive cohort of 17,816 patients who underwent coronary angiography for suspected coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients ₃₅176 ³⁷177 with a documented history of coronary heart disease were excluded. An additional 131 individuals were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative .5 46¹⁸⁰ coronary angiography results (Figure 1). ⁴⁸181 The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median ₅₄183 follow-up time was 631 [270, 972] days. Detailed baseline data are provided in Supplementary Table ⁵⁶-184 1. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

Kaplan-Meier method was employed to estimate the survival without various adverse events for the
total study population (Supplementary Figure 1).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (Supplementary Table 1). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (Figure 2A). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (Figure 2B). These variables were incorporated into a Cox proportional hazards regression model, with results presented in Table 1. All models satisfied proportional hazards assumptions (global test p=0.057). A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(Figure 3). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

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Table 1. Prediction of event-free survival probability using the Cox proportional hazards

regression r	nodel based	on LASSO	regression.
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Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	< 0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	< 0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	< 0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	< 0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase;
NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

12 Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75, 0.77, and 0.78, respectively (**figure 4**).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-

60220 degree line, indicating that predicted survival closely matches observed survival and demonstrating
good model calibration.

Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in **Figure 6**, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

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1 Risk stratification

Considering that the study population consists of low-risk patients with non-obstructive coronary artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves depicting event-free survival were created for the two risk groups in the training and validation sets (**Figure 7**). Furthermore, MACE-event free survival of these groups is shown in **Supplementary Figure 2**. These results consistently demonstrated the model's efficacy in patient risk stratification.

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Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic information, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [30]. However, research has

consistently shown that following diagnostic assessments like coronary angiography, approximately 50% of patients do not exhibit obstructive coronary artery stenosis [5,16,24,31]. Traditionally, such patients were often considered to have a favorable prognosis and no significant cardiac conditions , potentially resulting in the omission of further diagnostic measures and therapeutic interventions [32– 34]. However, recent research has indicated that these patients face a significantly elevated risk of adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among female ANOCA patients [21,35,36]. Other studies have also demonstrated that ANOCA patients, regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to the general population[16,31,37].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [31]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

280 While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

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with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who
require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent
review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various
underlying causes, such as coronary microvascular dysfunction, microvascular spasm, endothelial
dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,38], emphasizing the critical
importance of identifying high-risk ANOCA patients to optimize their further management.
Current research on factors related to adverse outcomes in the ANOCA population is limited. One
study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict
favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of
conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study
solely relied solely on pretest clinical data and accessed coronary arteries through CCTA [18]. In

contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [39,40].

Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinasetype plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

studies conducted comprehensive screening of clinical variables or developed a predictive model. After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [41]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [42,43]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [44]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [45,46]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [47-50]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [51]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [52–55].

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Our predictive model also considered echocardiographic parameters. Echocardiography is a 56³²¹ noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive ⁵⁸322 insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included.

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Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [56-59]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [60,61].

Limitations

This study has several limitations. First, the retrospective design precludes control of treatment strategies and introduces potential selection bias. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, the inability to subclassify ANOCA patients into those with versus without atherosclerosis represents an important limitation, as pathophysiological differences between these cohorts may contribute to population heterogeneity. However, this aligns with current guideline definitions, and future studies incorporating intracoronary imaging could refine risk stratification. Finally, while the predictive model developed from single-center data has not yet undergone external validation, internal validation confirmed its robust discrimination and calibration, indicating strong performance within the original cohort.

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Conclusion)

In summary, we conducted a comprehensive evaluation of clinically accessible variables and 3 successfully developed a predictive model for assessing adverse outcomes in angina patients with 4 suspected CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips 5 clinicians with a valuable tool for risk stratification in ANOCA patients, allowing for optimized 5 7 management and treatment strategies aimed at improving patient outcomes.

List of abbreviations 0

ANOCA, angina with nonobstructive coronary arteries

MI, myocardial infarction 2

PCI, percutaneous coronary intervention 3

CABG, coronary-artery bypass grafting 4

5 MACE, major adverse cardiovascular events

ALT, alanine transaminase

AST, aspartate transaminase

8 NT-proBNP, N-terminal pro-B-type natriuretic peptide

LVEF, left ventricular ejection fraction 9

AUC, area under the curve

CAD, coronary artery disease

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1 2	
3 4 362	CAG, coronary angiography
5 6 7 363	CCTA coronary computed tomography angiography
9 505 8 9	cerre, coronary compared comography angrography
10 ³⁶⁴	HDL-C, high-density lipoprotein cholesterol
¹² 365 13	SD, standard deviation
14 15366 16	IQR, interquartile range
17 18 ³⁶⁷	VIF, variance inflation factor
19 20 ₃₆₈ 21	
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35 36373 37	Medical University.
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43 43 44	Data availability statement
45 46 _{2.76}	The original data supporting the findings of this study can be obtained from the corresponding outfor
47 ⁵⁷⁰ 48	The original data supporting the findings of this study can be obtained from the corresponding author
49377 50 51 52378 53	upon reasonable request.
54 55 56379 57	Contributors
58 59 ₃₈₀ 60 ³⁸⁰	L.Z. Conceptualization, Investigation, Methodology, Data curation, Software, Formal analysis,

Visualization, Writing – original draft. Z.K.X. Investigation, Data curation, Formal analysis, Writing - review and editing. X.W. Methodology, Writing - review and editing. J.K.Z. Methodology, Writing - review and editing. S.T.H. Data curation, Writing - review and editing. Y.K.Z. Data curation, Writing - review and editing. T.S.G. Data curation, Writing - review and editing. T.L. Supervision, Validation, editing. S.W.R. Supervision, Writing – review and Validation, Funding acquisition, Writing – review and editing. K.Y.C. Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review and editing. All authors approved the final manuscript. K.Y.C. is responsible for the overall content as guarantor.

0 Competing interests

This study received infrastructure support from Tianjin Medical University. The funding organization played no role in study design, data collection, analysis, interpretation, manuscript preparation, or publication decisions. All authors declare no additional competing interests.

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References

Hoorweg BB, Willemsen RT, Cleef LE, *et al.* Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart Br Card Soc.* 2017;103:1727–32. doi: 10.1136/heartjnl 2016-310905

2 3 402 Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A 2 4 5 403 Report From the American Heart Association. Circulation. 2022;145:e153-639. doi: 6 404 10.1161/CIR.000000000001052 7 8 405 Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline 3 9 10406 for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart 11407 Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. 12 13⁴⁰⁸ Circulation. 2023;148:e9-119. doi: 10.1161/CIR.00000000001168 14 15409 Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline 4 16410 for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive 17 18411 Summary: A Report of the American College of Cardiology Foundation/American Heart 19412 Association Task Force on Practice Guidelines, and the American College of Physicians, American ²⁰413 21 Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for 22414 Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 23415 2012;126:3097-137. doi: 10.1161/CIR.0b013e3182776f83 24 ²⁵416 5 Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N 26 27417 Engl J Med. 2010;362:886-95. doi: 10.1056/NEJMoa0907272 28 29418 6 Rahman H, Corcoran D, Aetesam-Ur-Rahman M, et al. Diagnosis of patients with angina and non-³⁰ 31</sub>419 obstructive coronary disease in the catheter laboratory. Heart Br Card Soc. 2019;105:1536-42. 32420 doi: 10.1136/heartjnl-2019-315042 33 ³⁴421 Samuels BA, Shah SM, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 1-7 ³⁵ 36⁴²² Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 37423 2023;82:1245-63. doi: 10.1016/j.jacc.2023.06.043 38 ³⁹424 Shaw LJ, Merz CNB, Pepine CJ, et al. The economic burden of angina in women with suspected 8 40 41⁴⁰425 ischemic heart disease: results from the National Institutes of Health--National Heart, Lung, and 42426 Blood Institute--sponsored Women's Ischemia Syndrome Evaluation. Circulation. 2006;114:894-⁴³427 904. doi: 10.1161/CIRCULATIONAHA.105.609990 44 45 46428 9 Gulati M, Khan N, George M, *et al.* Ischemia with no obstructive coronary artery disease (INOCA): 47429 A patient self-report quality of life survey from INOCA international. Int J Cardiol. 2023;371:28-48₄₃430 39. doi: 10.1016/j.ijcard.2022.09.047 50 10 Takahashi T, Samuels BA, Li W, et al. Safety of Provocative Testing With Intracoronary 51431 52432 Acetylcholine and Implications for Standard Protocols. J Am Coll Cardiol. 2022;79:2367–78. doi: ⁵³433 10.1016/j.jacc.2022.03.385 55 56434 11 Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for 57435 coronary artery disease. N Engl J Med. 2015;372:1291-300. doi: 10.1056/NEJMoa1415516 58 59 60436 12 Udelson JE, Kelsey MD, Nanna MG, et al. Deferred Testing in Stable Outpatients With Suspected

Page 25 of 42

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2 3 427		Comment Artem Discours A Dress if a Grandam Analysis of the DDECICE Dandamind
4 43 /		Clinical Trial IAMA Condict Debliched Online First 22 Accest 2022
5 438		Clinical Irial. JAMA Caratol. Published Online First: 23 August 2023. doi: 10.1001/jeuropaulie.2022.2014
6 439 7		10.1001/jamacardio.2023.2614
⁸ 440	13	Gulati M Levy PD Mukheriee D et al 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR
9 ¹¹⁰	10	Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of
11/1/2		Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines
$12_{1/2}$		Circulation 2021:144:o268 454 doi: 10.1161/CIP.0000000000000000
13445		Circulation. 2021,144.6508–454. doi: 10.1101/CIK.00000000000000029
14 15444	14	Knuuti J Wiins W Saraste A <i>et al.</i> 2019 ESC Guidelines for the diagnosis and management of
16445		chronic coronary syndromes <i>Eur Heart I</i> 2020:41:407–77 doi: 10.1093/eurhearti/ehz425
17		enfonce coronary synchonics. Dar freurro. 2020, 11:107 77. doi: 10.1095/curreary/enz/25
18 19446	15	Jordan KP, Timmis A, Croft P, <i>et al.</i> Prognosis of undiagnosed chest pain: linked electronic health
20447		record cohort study. <i>BMJ</i> . 2017:357:i1194. doi: 10.1136/bmi.i1194
21		
²² 448	16	Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive
23 24449		coronary artery disease is associated with increased risks of major adverse cardiovascular events.
25450		Eur Heart J. 2012;33:734-44. doi: 10.1093/eurheartj/ehr331
26		
²⁷ ₂₈ 451	17	Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women
29452		with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome
30453		Evaluation Study and the St James Women Take Heart Project. Arch Intern Med. 2009;169:843-
$^{31}_{22}454$		50. doi: 10.1001/archinternmed.2009.50
32 33		
34455	18	Fordyce CB, Douglas PS, Roberts RS, et al. Identification of Patients With Stable Chest Pain
³⁵ 456		Deriving Minimal Value From Noninvasive Testing: The PROMISE Minimal-Risk Tool, A
³⁶ 37457		Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiol. 2017;2:400-8. doi:
38458		10.1001/jamacardio.2016.5501
39		
⁴⁰ 459	19	Al-Badri A, Tahhan AS, Sabbak N, et al. Soluble Urokinase-Type Plasminogen Activator
41 42 ⁴⁶⁰		Receptor and High-Sensitivity Troponin Levels Predict Outcomes in Nonobstructive Coronary
43461		Artery Disease. J Am Heart Assoc. 2020;9:e015515. doi: 10.1161/JAHA.119.015515
44 45		
⁴³ 462 46	20	Mansour M, Radaideh Q, Alaiwah MN, et al. Major adverse cardiac events in symptomatic women
47463		with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART.
48464		Int J Cardiovasc Imaging. 2022;38:683–93. doi: 10.1007/s10554-021-02429-3
49 50 . c -	0.1	
51465	21	Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and
52466		symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart,
53467 54		Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE)
55468		angiographic core laboratory. Am Heart J. 2013;166:134–41. doi: 10.1016/j.ahj.2013.04.002
56	22	Sadlak T. Harranyini D. Cook Wints C. et al Dradistad warres showed weight about 1
5/409 58470	22	Seulak 1, Herscovici K, Cook-wiens G, <i>et al.</i> Predicted versus observed major adverse cardiac
59, <u> </u>		event risk in women with evidence of ischemia and no obstructive coronary artery disease: A report
60 ^{47/1}		trom WISE (women's ischemia syndrome evaluation). J Am Heart Assoc. 2020;9:e013234. doi:

³ 472 10.1161/JAHA.119.013234

1 2

- ⁵ 6 473
 ⁶ 473
 ⁷ 474
 ⁸ 475
 ⁸ 475
 ⁸ 23 Collins GS, Reitsma JB, Altman DG, *et al.* Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594. doi: 10.1136/bmj.g7594
- Bairey Merz CN, Pepine CJ, Walsh MN, *et al.* Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. *Circulation*. 2017;135:1075–92. doi: 10.1161/CIRCULATIONAHA.116.024534
- 15
 16479 25 K T, Js A, As J, *et al.* Fourth universal definition of myocardial infarction (2018). *J Am Coll*17480 *Cardiol.* 2018;72. doi: 10.1016/j.jacc.2018.08.1038
- 19 20481 26 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients 21482 with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ²²483 ischemic stroke: a guideline for healthcare professionals from the American heart 23 24484 association/american stroke association. Stroke. 2019;50:e344-418. doi: 25485 10.1161/STR.000000000000211 26
- 27 28
 27 Mansour M, Radaideh Q, Alaiwah MN, *et al.* Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: Pooled analysis from PROMISE and SCOT-HEART. *Int J Cardiovasc Imaging.* 2022;38:683–93. doi: 10.1007/s10554-021-02429-3
- Al-Badri A, Tahhan AS, Sabbak N, *et al.* Soluble urokinase-type plasminogen activator receptor and high-sensitivity troponin levels predict outcomes in nonobstructive coronary artery disease. J *Am Heart Assoc.* 2020;9:e015515. doi: 10.1161/JAHA.119.015515
- Johnson BD, Shaw LJ, Pepine CJ, *et al.* Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: Results from the NIH-NHLBI-sponsored women's ischaemia syndrome evaluation (WISE) study. *Eur Heart J.* 2006;27:1408–15. doi: 10.1093/eurheartj/ehl040
- 43
 44496
 45
 497
 46
 30 Douglas PS, Hoffmann U, Patel MR, *et al.* Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med.* 2015;372:1291–300. doi: 10.1056/NEJMoa1415516
- 47
 48498 31 Maddox TM, Stanislawski MA, Grunwald GK, *et al.* Nonobstructive coronary artery disease and
 49499 risk of myocardial infarction. *JAMA*. 2014;312:1754–63. doi: 10.1001/jama.2014.14681
- ⁵¹500
 32 Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy.
 JAMA. 2005;293:477–84. doi: 10.1001/jama.293.4.477
- Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol*. 1995;25:1013–8. doi: 10.1016/0735-1097(94)00519-v
- ⁶⁰505 34 Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left

Page 27 of 42

1 2

34

BMJ Open

- Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.
- ³ 506 4 507 5 507 6 ventricular function. Long-term follow-up study. *J Am Coll Cardiol*. 1995;25:807–14. doi: 10.1016/0735-1097(94)00507-M
- ⁷ 508
 ⁸ 509
 ⁸ 509
 ⁹ 509
- 13 14512 36 Kenkre TS, Malhotra P, Johnson BD, *et al.* Ten-Year Mortality in the WISE Study (Women's Ischemia Syndrome Evaluation). *Circ Cardiovasc Qual Outcomes*. 2017;10:e003863. doi: 10.1161/CIRCOUTCOMES.116.003863
- ¹⁸₁₉515
 ¹⁸₁₉515
 ¹⁸₁₉515
 ¹⁸₁₉515
 ¹⁸₁₉515
 ¹⁰<sub>101016/j.ahj.2013.03.015
 ¹⁰₂₂517
 ¹⁰<sub>101016/j.ahj.2013.03.015
 </sub></sub>
- 38 Smilowitz NR, Prasad M, Widmer RJ, *et al.* Comprehensive Management of ANOCA, Part 2 Program Development, Treatment, and Research Initiatives: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2023;82:1264–79. doi: 10.1016/j.jacc.2023.06.044
- 39 Sedlak T, Herscovici R, Cook-Wiens G, *et al.* Predicted Versus Observed Major Adverse Cardiac
 Sedlak T, Herscovici R, Cook-Wiens G, *et al.* Predicted Versus Observed Major Adverse Cardiac
 Event Risk in Women With Evidence of Ischemia and No Obstructive Coronary Artery Disease:
 A Report From WISE (Women's Ischemia Syndrome Evaluation). *J Am Heart Assoc.*2020;9:e013234. doi: 10.1161/JAHA.119.013234
- ³⁵525
 40 Moreau P, d'Uscio LV, Lüscher TF. Structure and reactivity of small arteries in aging. *Cardiovasc Res.* 1998;37:247–53. doi: 10.1016/s0008-6363(97)00225-3
- ³⁸
 ³⁹⁵²⁷ 41 Rymer JA, Rao SV. Anemia and coronary artery disease: pathophysiology, prognosis, and treatment. *Coron Artery Dis.* 2018;29:161–7. doi: 10.1097/MCA.00000000000598
- 42 43529
 42 Gan T, Hu J, Liu W, *et al.* Causal Association Between Anemia and Cardiovascular Disease: A 244530
 44530
 45531
 46
 42 Gan T, Hu J, Liu W, *et al.* Causal Association Between Anemia and Cardiovascular Disease: A 245
 46
- 47
 43 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated
 49533 with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure.
 50/534 *Circulation*. 2003;107:223–5. doi: 10.1161/01.cir.0000052622.51963.fc
- 44 Herzog CA, Asinger RW, Berger AK, *et al.* Cardiovascular disease in chronic kidney disease. A
 clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.*2011;80:572–86. doi: 10.1038/ki.2011.223
- Liu F, Ma G, Tong C, *et al.* Elevated blood urea nitrogen-to-creatinine ratio increased the risk of
 Coronary Artery Disease in patients living with type 2 diabetes mellitus. *BMC Endocr Disord.*

4 5

6

8

9

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540 2022;22:50. doi: 10.1186/s12902-022-00954-3 541 46 Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of 7 542 subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced 543 glomerular filtration rates. J Am Coll Cardiol. 2005;45:1781-6. doi: 10.1016/j.jacc.2005.02.068 10 11544 47 He X, Liu C, Chen Y, et al. Risk of Cardiovascular Mortality Associated With Serum Sodium and 12545 2018;34:999-1003. Chloride in the General Population. Can JCardiol. 13 14⁵⁴⁶ 10.1016/j.cjca.2018.03.013 15 16547 48 Wannamethee SG, Shaper AG, Lennon L, et al. Mild hyponatremia, hypernatremia and incident 17548 cardiovascular disease and mortality in older men: A population-based cohort study. Nutr Metab 18 19549 Cardiovasc Dis NMCD. 2016;26:12-9. doi: 10.1016/j.numecd.2015.07.008 20 21550 49 Ahn SY, Park YS, Lee SW, et al. Association Between Small Decrease in Serum Sodium ²²551 Concentration within the Normal Range and All-Cause and Cardiovascular Mortality in Elderly 23 23 24552 Adults over 5 Years. J Am Geriatr Soc. 2016;64:510-7. doi: 10.1111/jgs.13937 25 26553 50 Sajadieh A, Binici Z, Mouridsen MR, et al. Mild hyponatremia carries a poor prognosis in ²⁷554 community subjects. Am J Med. 2009;122:679-86. doi: 10.1016/j.amjmed.2008.11.033 29 30555 51 Doust JA, Pietrzak E, Dobson A, et al. How well does B-type natriuretic peptide predict death and 31556 cardiac events in patients with heart failure: systematic review. BMJ. 2005;330:625. doi: ³² 33⁵⁵⁷ 10.1136/bmj.330.7492.625 34 35558 52 McKie PM, Rodeheffer RJ, Cataliotti A, et al. Amino-terminal pro-B-type natriuretic peptide and 36559 B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of ³⁷ 38⁵⁶⁰ Tex 1979. heart failure. Hypertens Dallas 2006;47:874-80. 39561 10.1161/01.HYP.0000216794.24161.8c 40 ⁴¹562 53 Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of 42 43⁴²563 cardiovascular events and death. N Engl J Med. 2004;350:655-63. doi: 10.1056/NEJMoa031994 44 45564 54 Rosenberg J, Schou M, Gustafsson F, et al. Prognostic threshold levels of NT-proBNP testing in 46 47 565 primary care. Eur Heart J. 2009;30:66-73. doi: 10.1093/eurheartj/ehn525 48 49566 55 Kistorp C, Raymond I, Pedersen F, et al. N-terminal pro-brain natriuretic peptide, C-reactive 50567 protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older ⁵¹568 adults. JAMA. 2005;293:1609-16. doi: 10.1001/jama.293.13.1609 53 54569 56 Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and 55570 Clinical Significance. JACC 2017;10:65-77. Cardiovasc Imaging. ⁵⁶571 10.1016/j.jcmg.2016.11.003 58 59572 57 Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk 60573 factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995;98:476-84. doi: 25

Page 29 of 42

1	
$\frac{2}{3}{4}$ 574	10.1016/S0002-9343(99)80348-9
5 6 575 7 576 8 577 10578	58 Marsan NA, Maffessanti F, Tamborini G, <i>et al.</i> Left atrial reverse remodeling and functional improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-dimensional echocardiography study. <i>Am Heart J.</i> 2011;161:314–21. doi: 10.1016/j.ahj.2010.10.029
12579 13 14 ⁵ 80 15581 16	59Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110:1042–6. doi: 10.1161/01.CIR.0000140263.20897.42
17582 18 19583 20584 21585 22 23586 24587 25	60 Bozkurt B, Coats AJS, Tsutsui H, <i>et al.</i> Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. <i>Eur J Heart Fail.</i> 2021;23:352–80. doi: 10.1002/ejhf.2115
26 27 28589 29590 30 31 591 32 33592 34	61 Heidenreich PA, Bozkurt B, Aguilar D, <i>et al.</i> 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. <i>Circulation</i> . 2022;145:e895–1032. doi: 10.1161/CIR.00000000001063
35 36593	Figure and table
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³⁹ 594 40	Figure 1. Flowchart of study participation. CAD, coronary artery disease.
41 42595 43	
44 45596 46	Figure 2. Variable Selection Based on LASSO Regression. (A) Variation Characteristics of Variable
47 48 597	Coefficients; (B) Selection Process of Optimal λ Value in LASSO Regression Model Using Cross-
50598 51 52 53599 54	Validation.
55 56600	Figure 3. Nomogram for predicting the probability of 1-, 2-, and 3-year event-free survival of
57 58601 59	ANOCA patients as assessed by coronary angiography. ALT, alanine transaminase; AST, aspartate

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3 4 602 5	transaminase; LVEF, left ventricular ejection fraction.
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8 9 (04	Figure 4. Desciver an experimenting shares deviating survey for the 1-2 and 2 was review and reints of
10 ⁶⁰⁴ 11	Figure 4. Receiver operating characteristic curve for the 1-, 2-, and 3-year primary endpoints of
12 ₆₀₅ 13 14 15606	the nomogram in the training set (A) and validation set (B). AUC, area under the curve.
16 17 18 ⁶⁰⁷ 19	Figure 5. Calibration plot of predicted 1-, 2-, and 3-year event-free survival based on the
²⁰ 608 21 22 23609	nomogram in the training set and validation set. (A–C) Training set; (D–F) Validation set.
24 25	
26610 27	Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation
28 29 ⁶¹¹ 30	cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit.
³¹ 612 32	The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray
34613 35	line represents the net benefit of not treating any patients. The curve in the middle represents the
36 37614	nomogram.
38	
³⁹ 615	
42616 43	Figure 7. Kaplan-Meier curves for primary endpoint event-free survival in the low-risk and
44 45617 46 47 48 ⁶¹⁸	high-risk groups in the training set (A) and validation set (B).
49 50619 51 52	Supplementary Table 1. Clinical data of the total population, training set and validation set.
53620 54 55 5621	Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the
50°21 57 58	Supprementary righter is breaching of unterent auverse outcomes in the
59 ⁶²²	total population.
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Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and hig
risk groups in the training set (A) and validation set (B).





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Supplementary Table 1. Clinical data of the total population, training set and validation set.

Variable	Total	Train set	Validation set	p value
	N=5934	N=4452	N=1482	
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798
WBC, 10 ⁹ /L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831
Serum creatinine, µmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748
Uric acid, µmol/L	335 (100)	335 (101)	335 (99.0)	0.889
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968	
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406	
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353	
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169	
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341	
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157	
Total bilirubin, µmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257	
Indirect Bilirubin, µmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242	
Direct Bilirubin, µmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611	
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820	
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919	
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485	
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083	
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498	
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627	
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536	
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415	
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529	
D-Dimer, µg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110	
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579	
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331	

Variable	Total	Train set	Validation set	p value	
	N=5934	N=4452	N=1482		
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373	
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737	
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623	
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486	
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512	
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816	
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189	
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156	
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611	
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523	

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.



Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population

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Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).