

Cardiovascular Reviews

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Cardiovascular Reviews

Focus and Scope

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Table of Contents

- 1 Analysis of the Predictive Value of Neutrophil-to-Albumin Ratio on the Prognosis of Patients with Acute Non-ST-Segment Elevation Myocardial Infarction**
Hongxia Ma, Yan He, Yan Li, Yuntao Sun
- 9 Antithrombotic Strategies and Complication Management in Paroxysmal Atrial Fibrillation Complicated by Mesenteric Artery Embolism: A Case Report and Literature Review of an Elderly Patient**
Guojian Lin, Shijin Chen, Xinxin Liu, Qian Yang
- 17 The Application Value of Speckle Tracking Imaging in Patients with Coronary Artery Disease without Regional Wall Motion Abnormalities**
Yu Dong, Ao Sun, Qian Hu, Tong Lin, Wenxiu Wang, Qingxiong Yue
- 26 Analysis of the Improvement of Inflammatory Factor Levels in Patients with Coronary Heart Disease and Hyperlipidemia Treated with Alirocumab and Atorvastatin**
Zhuo Li, Yuan Liu
- 33 Twenty-Five Years of Strain Imaging in Cardiac Function Assessment: Bibliometrics and Emerging Frontiers (2000–2025)**
Xiaodi Chen, Zhiyang Lv
- 45 Causal Association Between Immune Cells and Cardiac Arrest: A Mendelian Randomization Study**
Yue Liu, Yun Zhu
- 56 Colchicine and Cardiovascular Disease: Mechanisms, Clinical Evidence, and Therapeutic Perspectives**
Zhiyang Lv, Xiaodi Chen, Qing Lu, Shifang Ding

Analysis of the Predictive Value of Neutrophil-to-Albumin Ratio on the Prognosis of Patients with Acute Non-ST-Segment Elevation Myocardial Infarction

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Abstract: *Objective:* To explore the predictive value of neutrophil-to-albumin ratio (NPAR) on the prognosis of patients with acute non-ST-segment elevation myocardial infarction (NSTEMI). *Methods:* A retrospective analysis was performed on the clinical data of 506 NSTEMI patients admitted between January 2018 and October 2024. The general information, laboratory test results, and prognosis of the two groups were compared. The NPAR value was calculated, and patients were divided into high, medium, and low NPAR groups based on tertiles. Multivariable Cox regression analysis was used to investigate the relationship between NPAR and prognosis, and ROC curves were plotted to evaluate the predictive performance of NPAR. *Results:* The incidence of major adverse cardiovascular events (cardiac function) was significantly higher in the high NPAR group than in the medium and low NPAR groups ($P < 0.05$). Multivariable Cox regression analysis showed that significant changes in NPAR in the high NPAR group were important predictors of prognosis for NSTEMI patients. The results of this study indicate that significant changes in NPAR values in the high NPAR group are associated with mortality. *Conclusion:* NPAR serves as a significant prognostic predictor in NSTEMI patients. Elevated NPAR levels are strongly associated with increased mortality risk, supporting its utility in early risk stratification and clinical decision-making.

Keywords: Neutrophil percentage; Albumin; Acute non-ST-segment elevation myocardial infarction; Prognosis; Predictive value

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1. Introduction

Acute non-ST-segment elevation myocardial infarction (NSTEMI) is a significant type of acute coronary syndrome, with its incidence rate increasing year by year, posing a severe threat to human health. Accurate assessment of the prognosis of NSTEMI patients is crucial for developing individualized treatment plans and improving patient outcomes. In recent years, growing research has indicated that inflammatory response and nutritional status play vital roles in the occurrence, development, and prognosis of NSTEMI.

The percentage of neutrophils is an important indicator reflecting the inflammatory state of the body, while the albumin level can effectively reflect the nutritional status of patients. The neutrophil percentage to albumin ratio (NPAR), as a novel comprehensive index of inflammation and nutrition, has demonstrated good predictive value in the prognosis evaluation of various diseases. However, research on the application of NPAR in predicting the prognosis of NSTEMI patients remains scarce. Therefore, this study aims to explore the predictive value of NPAR in the prognosis of NSTEMI patients, providing a new risk assessment tool for clinical practice.

2. Materials and methods

2.1. Clinical data

This study employs a retrospective cohort study method, selecting NSTEMI patients who were hospitalized in the Cardiovascular Department of our hospital from January 2018 to October 2024 as the research subjects. Inclusion criteria: (1) Meet the diagnostic criteria for NSTEMI; (2) Age ≥ 18 years old. Exclusion criteria: (1) Combined with severe infection, malignant tumor, or autoimmune disease; (2) Recent use of immunosuppressive agents or hormone therapy; (3) Severe liver and kidney dysfunction; (4) Patients with original or developing severe liver and kidney dysfunction or cachexia during the disease course. Finally, a total of 506 patients were included, consisting of 400 males and 106 females, with an average age of (61.5 ± 12.9) years old.

2.2. Data collection

Collect general information about the patients (age, gender, smoking history, history of hypertension, history of diabetes, etc.), laboratory test results (neutrophil percentage, albumin level, white blood cell count, neutrophil count, D-dimer, creatinine, urea nitrogen, triglycerides, high-density lipoprotein, low-density lipoprotein; cardiac function: left ventricular ejection fraction, Killip classification, GRACE score, TIMI risk score; treatment medications: aspirin, clopidogrel/ticagrelor, statins, etc.), prognosis, and time of death. Patients were divided into high NPAR, medium NPAR, and low NPAR groups based on tertiles.

2.3. Research indicators and follow-up methods

The primary endpoint of this study is all-cause mortality. Patients were followed up during hospitalization using the hospital information system and ward visits, and during discharge using outpatient clinic visits or telephone follow-ups.

2.4. Statistical methods

Statistical analysis was performed using SPSS 25.0 software. Measurement data are expressed as mean \pm standard deviation (SD), and comparisons between groups were made using the *t*-test. Count data are expressed as the number of cases (percentage), and comparisons between groups were made using the χ^2 test. Multivariable Cox regression analysis was used to analyze the relationship between NPAR and prognosis, and ROC curves were

drawn to evaluate the predictive performance of NPAR. A P -value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of general clinical baseline data of NSTEMI patients in different NPAR groups

Table 1. Comparison of baseline clinical characteristics of NSTEMI patients across different NPAR groups

	NPAR Grading						ANOVA Analysis	
	Low NPAR		Medium NPAR		High NPAR		F-value	P-value
	Mean	SD	Mean	SD	Mean	SD		
Admission WBC Count	7.97	2.48	8.28	2.46	9.49	3.28	14.121	0.000
Neutrophil Percentage (%)	55.9	8.5	70.3	6.7	79.0	6.6	421.680	0.000
Lymphocyte Count	2.81	1.22	1.78	0.51	1.33	0.50	146.495	0.000
D-Dimer	29.85	92.94	41.77	186.38	114.48	394.21	3.518	0.031
Creatinine	81.13	79.26	82.09	44.63	90.17	84.14	0.807	0.447
Blood Urea Nitrogen	5.97	2.16	6.19	3.31	6.96	3.51	4.827	0.008
Triglycerides	2.04	1.36	1.89	1.60	1.66	1.11	3.241	0.040
Cholesterol	4.60	1.04	4.71	1.16	4.36	1.18	4.008	0.019
Albumin	44.32	3.17	43.12	3.77	39.26	4.79	74.430	0.000
HDL	0.95	0.24	0.97	0.24	0.96	0.24	0.290	0.749
LDL	2.90	0.91	2.93	0.93	2.71	0.93	2.654	0.071
CK-MB	30.58	36.83	47.36	59.43	60.80	90.41	8.713	0.000
Troponin T	462.748	2239.086	841.840	6439.088	1553.869	6875.562	1.502	0.224
CRP	5.01	8.71	6.70	14.76	17.06	35.27	13.457	0.000
Cardiac Ultrasound: EF Value (%)	56.2	5.8	54.2	7.8	54.3	7.7	2.820	0.061
Rechecked Neutrophil Percentage (%)	62.0	9.0	67.3	7.9	71.3	9.4	46.455	0.000
Rechecked Albumin	39.80	2.67	39.34	3.18	36.95	4.32	29.965	0.000
GRACE Score	132.8	33.6	131.5	29.1	144.9	36.7	3.623	0.028
Survival Time	1050.1	674.4	1144.7	650.4	1009.9	703.1	1.747	0.175

The statistical analysis (**Table 1**) indicates significant differences between various grades for multiple biomarkers and clinical indicators such as neutrophil percentage, albumin, and CRP. In contrast, other indicators like creatinine and high-density lipoprotein did not show significant variations. These results suggest that certain indicators could serve as important references for disease grading and prognostic evaluation. Specifically, patients in the high NPAR group demonstrated higher abnormality levels in multiple indicators, indicating a more severe condition for this group, which may require more aggressive intervention and treatment.

3.2. Comparison of cumulative survival rates among patients in different NPAR groups

Among the different NPAR groups (low, medium, and high), there were no significant differences in survival

status (survival and death) ($\chi^2 = 2.659, p = 0.265$). Specifically, in the low NPAR group, 65 patients survived, and 85 patients died; in the medium NPAR group, 84 patients survived, and 57 patients died; in the high NPAR group, 72 patients survived, and 62 patients died. Although the number of survivors and deaths varied among the different groups, the chi-square test results showed that these differences did not reach statistical significance (p -value greater than 0.05) (**Table 2**).

Through the Chi-square test, this study failed to find significant differences in survival status among patients in different NPAR groups. This suggests that although differences in survival status are observed among different grades of patient populations, these differences may be coincidental or influenced by other unconsidered clinical factors. Overall, the NPAR grading seems to fail to significantly predict the survival status of patients, and further analysis may be needed in combination with other clinical indicators and treatment factors.

Table 2. Comparison of survival status among NSTEMI patients in different NPAR groups

Survival status	NPAR grouping			χ^2	P-value
	Low	Medium	High		
Survived	65	84	72	2.659	0.265
Deceased	85	57	62		

In the high NPAR group (**Table 3**), there was a significant difference in NPAR values between surviving and deceased patients ($t = -2.767, p = 0.006$). The mean NPAR value for surviving patients was 2.02 (standard deviation = 0.38), while the mean NPAR value for deceased patients was 2.29 (standard deviation = 0.44). This difference suggests that the NPAR values of deceased patients were significantly higher than those of surviving patients, indicating a possible negative correlation between dynamic changes in NPAR and prognosis in this group.

Table 3. Comparison of NPAR values between survivors and non-survivors in the high NPAR group

Survival outcome		Number of cases	Mean	Standard deviation	t	P
NPAR	0	152	2.02	0.38	-2.767	0.006
	1	17	2.29	0.44		

Through t-test analysis, the overall results showed that there were group differences in the relationship between dynamic changes in NPAR and patient prognosis. In the overall sample, the NPAR values of surviving patients were significantly higher than those of deceased patients, suggesting that NPAR, as a potential prognostic indicator, may have a certain predictive value. However, in the low NPAR and medium NPAR groups, there was no significant difference between NPAR values and patient prognosis, indicating that dynamic changes in NPAR within these groups failed to effectively distinguish between surviving and deceased patients.

It is worth noting that in the high NPAR group, the NPAR values of surviving patients were significantly lower than those of deceased patients, indicating that higher NPAR values in this group may be associated with a poorer prognosis. This result suggests that dynamic changes in NPAR may have different effects on patient prognosis in different groups, especially in the high NPAR group, where higher NPAR values may indicate worse survival outcomes.

Based on the above findings, dynamic changes in NPAR may have a certain predictive effect on prognosis

in certain subgroups. Especially in the high NPAR subgroup, significant changes in NPAR values are associated with death, while this relationship is not evident in other subgroups. Further research may need to explore the interaction of other variables with NPAR to more accurately predict patient prognosis.

4. Cox regression analysis of factors influencing all-cause death in NSTEMI patients

4.1.1. Omnibus test

The fit of the model was evaluated using the Omnibus test (**Table 4**). The results showed that the overall model had a chi-square value of 11.804 with 3 degrees of freedom and a significance level of 0.008, indicating that the overall fit of the model was statistically significant. Compared to the previous step, the model had a change in chi-square of 6.984 with 3 degrees of freedom and a significance level of 0.072, suggesting that the contribution of this step's changes to the model had not yet reached statistical significance. Despite this, the overall fit of the model still demonstrated some statistical significance.

Table 4. Omnibus test of model coefficients

-2 Log Likelihood	Overall (Score)			Change from Previous Step			Change from Previous Block		
	Chi-Square	df	Sig.	Chi-Square	df	Sig.	Chi-Square	df	Sig.
439.801	11.804	3	.008	6.984	3	.072	6.984	3	.072

Note: The starting block number is 1. Method = Input.

4.1.2. The impact of NPAR on all-cause death in NSTEMI patients

The results of Cox regression analysis (**Table 5**) showed that the effect of NPAR on all-cause mortality in NSTEMI patients was significant ($B=0.785$, $p=0.010$). The $\text{Exp}(B)$ value for this variable was 2.191, with a 95% confidence interval of [1.208, 3.977], indicating that for every one-unit increase in NPAR, the risk of all-cause death in patients increased by 2.191 times. Therefore, patients with higher NPAR values had a higher risk of death, suggesting that NPAR could serve as a potential prognostic indicator with a significant predictive role in all-cause mortality among NSTEMI patients.

Table 5. Cox regression analysis of the impact of NPAR on all-cause mortality in NSTEMI patients

	B	Std. Error	Wald	df	Sig.	Exp (B)	95.0% CI for Exp (B)	
							Lower	Upper
npar	0.785	0.304	6.657	1	.010	2.191	1.208	3.977
nparlevel	-	-	0.022	2	.989	-	-	-
nparlevel(1)	0.012	0.508	0.001	1	.982	1.012	0.374	2.739
nparlevel(2)	-0.048	0.421	0.013	1	.910	0.954	0.417	2.178

The results of Cox regression analysis demonstrated that dynamic changes in NPAR had a significant predictive effect on all-cause mortality in NSTEMI, with higher NPAR values associated with increased risk of death. However, NPAR grading did not significantly affect all-cause mortality, possibly indicating limited effectiveness in predicting death risk.

Based on the Exp(B) value, it was evident that every unit increase in NPAR significantly elevated the risk of all-cause death. This suggests that when considered as a continuous variable, NPAR has a stronger predictive ability for death, whereas its grading as a categorical variable may not provide sufficient risk differentiation. These findings imply that using the continuous variable NPAR to predict the prognosis of NSTEMI patients may be more accurate and effective in clinical practice.

Table 6. Multivariate cox regression analysis of factors associated with all-cause mortality in NSTEMI patients

		B	Standard error	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
Step1	HDL	4.313	1.480	8.489	1	.004	74.637	4.102	1357.981
Step 2	HDL	6.217	1.879	10.950	1	.001	501.357	12.613	19928.551
	Cardiac Ultrasound: EF	-0.155	0.048	10.157	1	.001	0.857	0.779	0.942
	Neutrophil %	-0.104	0.049	4.447	1	.035	0.901	0.819	0.993
Step 3	HDL	8.444	2.736	9.523	1	.002	4648.831	21.781	992233.938
	Cardiac Ultrasound: EF	-0.229	0.071	10.273	1	.001	0.795	0.691	0.915
	Neutrophil %	-0.150	0.058	6.682	1	.010	0.861	0.768	0.964
Step 4	HDL	7.222	2.576	7.858	1	.005	1369.616	8.782	213607.426
	LDL	-1.431	0.733	3.807	1	.051	0.239	0.057	1.007
	Cardiac Ultrasound: EF	-0.267	0.081	10.752	1	.001	0.766	0.653	0.898

Through stepwise Cox regression analysis (**Table 6**), this study found that the following laboratory examination indicators significantly affect all-cause death in NSTEMI patients:

- (1) High-density lipoprotein (HDL) significantly reduces the risk of death, with an Exp(B) value of 74.637, indicating that an increase in HDL may be closely related to a reduction in the risk of death.
- (2) The EF value from echocardiography is a negative influencing factor. For every 1-unit decrease in EF value, the risk of death increases by approximately 14%.
- (3) The percentage of neutrophils is negatively correlated with the risk of death, suggesting that a higher percentage of neutrophils may reflect an increase in the level of inflammation in patients, which is associated with a higher risk of death.
- (4) Although low-density lipoprotein (LDL) did not reach strict statistical significance ($p = 0.051$), it still showed a strong negative correlation, suggesting that LDL levels may have some predictive value for the risk of death in certain cases.

These findings indicate that laboratory examination indicators have important predictive value for the prognosis of NSTEMI patients, and in particular, high-density lipoprotein and echocardiography EF values may become important reference indicators for evaluating patients' risk of death.

5. Discussion

The NPAR, as the ratio of neutrophil percentage to albumin, can simultaneously reflect the inflammatory status and nutritional status of the body. An increase in neutrophil percentage suggests a strong inflammatory

response in the body, while a low albumin level indicates malnutrition or an inflammatory consumption state. In NSTEMI patients, persistent inflammatory responses may lead to plaque instability and myocardial injury, while malnutrition can weaken the body's repair capabilities, thereby affecting patient prognosis^[1]. Therefore, NPAR can comprehensively evaluate the risk of NSTEMI patients from both inflammatory and nutritional dimensions^[2], providing a simple and effective prognostic prediction tool for clinical practice.

The results of this study showed that NPAR is significantly associated with the prognosis of NSTEMI patients. The incidence of heart failure in the high NPAR group was significantly higher than that in the low NPAR group. Multivariate Cox regression analysis further confirmed that NPAR is an independent predictor of prognosis in NSTEMI patients. This finding is consistent with previous research results^[3-6] in other cardiovascular diseases, supporting the clinical value of NPAR as a comprehensive inflammatory-nutritional indicator in the prognostic evaluation of cardiovascular diseases.

Dynamic changes in NPAR may have predictive effects on the prognosis of certain subgroups of patients, especially in the high NPAR group, where changes in NPAR values are significantly associated with the risk of death. Cox regression analysis in this study showed that dynamic changes in NPAR have a significant impact on all-cause mortality in NSTEMI patients, while the effect of NPAR grading on all-cause mortality did not reach statistical significance. Therefore, using NPAR as a continuous variable may be more beneficial for predicting the risk of death in NSTEMI patients, providing an important reference for clinical prognostic evaluation. Further research can explore the combined application of NPAR with other clinical indicators to improve the accuracy of prognostic prediction.

Through stepwise Cox regression analysis, this study confirmed the predictive value of multiple laboratory indicators, including high-density lipoprotein, echocardiographic EF value, and neutrophil percentage, for all-cause mortality in NSTEMI patients. These indicators not only effectively assess the risk of death but also provide an important basis for clinical decision-making. Future research can further explore the optimal use of combinations of these laboratory indicators for prognostic evaluation.

This study innovatively combined the use of neutrophil percentage and albumin indicators, which reflect different pathophysiological mechanisms, to multi-dimensionally evaluate the severity of NSTEMI patients' conditions. These two indicators are simple to detect and highly accessible, facilitating early risk stratification of NSTEMI patients.

However, this study has limitations. As a small-sample, single-center retrospective study, the level of evidence is relatively low and needs to be validated through large-sample, multicenter studies.

6. Conclusion

In summary, NPAR is an important predictor of prognosis for NSTEMI patients. In the high NPAR level group, changes in NPAR values are significantly correlated with the risk of death. NPAR can be used for early risk stratification of NSTEMI patients, providing a basis for clinical decision-making and facilitating communication with patients' families.

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Antithrombotic Strategies and Complication Management in Paroxysmal Atrial Fibrillation Complicated by Mesenteric Artery Embolism: A Case Report and Literature Review of an Elderly Patient

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Abstract: *Objective:* To explore antithrombotic strategy selection and bleeding complication management in patients with paroxysmal atrial fibrillation (AF) complicated by acute mesenteric artery embolism (AME). *Methods:* The diagnosis and treatment process of an 84-year-old patient with AF complicated by AME was reviewed, and the balancing strategy between antithrombotic therapy and reperfusion injury was analyzed in conjunction with the literature. *Results:* The patient developed intestinal bleeding and abdominal wall hematoma after interventional thrombectomy, and the risks of thrombosis and bleeding were ultimately controlled through a dual antithrombotic regimen of rivaroxaban combined with clopidogrel. *Conclusion:* For AF complicated by AME, individualized weighing of thromboembolic and bleeding risks is necessary, and multidisciplinary collaboration and dynamic monitoring are crucial for optimizing treatment.

Keywords: Paroxysmal atrial fibrillation; Mesenteric artery embolism; Anticoagulant therapy; Reperfusion injury; Bleeding risk management

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1. Introduction

Acute mesenteric artery embolism can lead to acute intestinal ischemic necrosis and even life-threatening conditions. Patients often present with sudden abdominal pain, nausea, vomiting, diarrhea, and gastrointestinal bleeding. However, the abdomen may feel soft, even without tenderness, making diagnosis challenging and resulting in a high clinical mortality rate. When acute mesenteric artery embolism is combined with paroxysmal atrial fibrillation, the condition can be further exacerbated. It is crucial to provide timely and accurate diagnosis,

select an appropriate antithrombotic strategy, and implement scientifically sound complication management. This article analyzes the clinical diagnosis and treatment of an elderly patient with paroxysmal atrial fibrillation complicated by mesenteric artery embolism. The report is as follows.

2. Case information and diagnosis/treatment course

The patient, an 84-year-old female, was admitted at 15:55 on October 26, 2022, due to “sudden abdominal pain for 3 hours.” On the day of admission, the patient had consumed leftover food at noon and developed persistent colicky pain in the epigastric region around 13:00 without obvious inducement. The pain did not radiate to other areas and was accompanied by profuse sweating and palpitations. Subsequently, she had two episodes of diarrhea, characterized by yellow watery stools. There was no nausea, vomiting, fever, chest pain, chest tightness, or bloody stools. She was admitted to the hospital with a preliminary diagnosis of “abdominal pain under investigation.”

2.1. Past medical history

The patient had a history of coronary heart disease, paroxysmal atrial fibrillation, incomplete right bundle branch block, type 2 diabetes mellitus, hyperthyroidism, chronic kidney disease, hyperuricemia, hyperlipidemia, severe osteoporosis, lumbar vertebral compression fracture, thrombocytosis, and left lower extremity venous thrombosis. In July 2021, she underwent “percutaneous vertebroplasty for L2 vertebral compression fracture.” She had no history of drug allergies.

2.2. Physical examination on admission

Vital signs were stable: temperature 36.0 °C, pulse 72 beats/min, respiratory rate 19 breaths/min, blood pressure 180/71 mmHg. No significant abnormalities were found on cardiopulmonary examination. The abdomen was flat and soft, with mild tenderness in the upper abdomen but no rebound tenderness. Bowel sounds were slightly hyperactive, approximately 7 times/min.

2.3. Auxiliary examinations

A 12-lead electrocardiogram showed atrial fibrillation (**Figure 1**). D-dimer was significantly elevated (5515.29 ng/mL). Myocardial enzyme profile indicated lactate dehydrogenase 503 U/L and α -hydroxybutyrate dehydrogenase 357 U/L. Renal function tests showed urea nitrogen 11.42 mmol/L, creatinine 110 μ mol/L, and uric acid 522 μ mol/L.

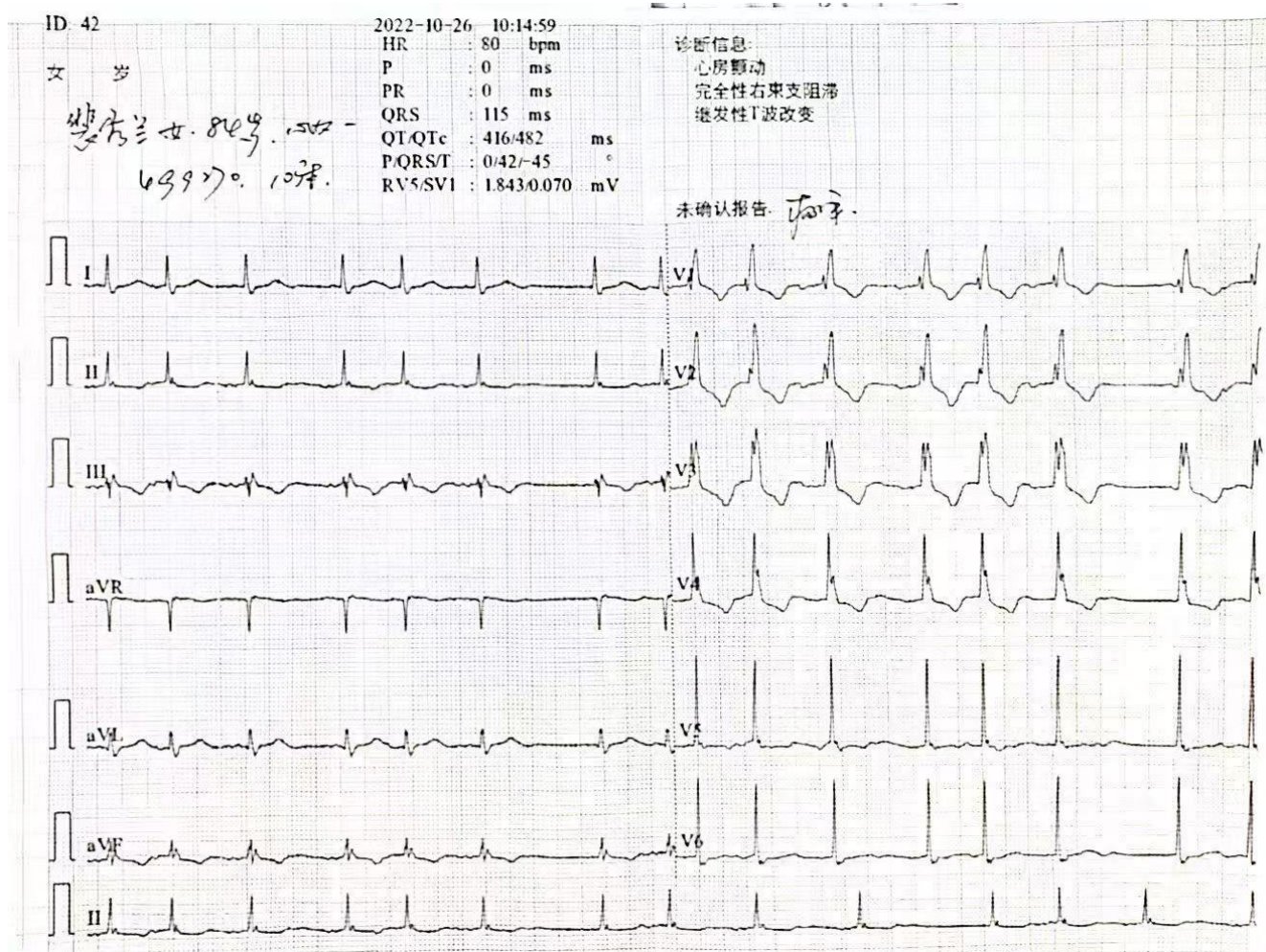


Figure 1. Twelve-lead electrocardiogram at admission.

2.4. Preliminary diagnosis

Abdominal pain under investigation: acute gastroenteritis? Ischemic bowel disease? Intestinal spasm? Empirical treatment was initiated, including anti-infection therapy, antispasmodics, acid suppression and gastric protection, as well as fluid replacement. The patient's abdominal pain symptoms were temporarily alleviated.

Around 18:00 on October 27, the patient experienced recurrent abdominal pain accompanied by abdominal distension. Physical examination revealed absent bowel sounds. Emergency computed tomography angiography (CTA) of the abdominal aorta indicated: (1) Thrombosis in the superior mesenteric artery, involving the jejunal and ileal arteries, ileal artery, and ileocolic artery; (2) Significant dilation of the small intestine with air-fluid levels, suggesting intestinal paralysis; (3) Atherosclerosis of the abdominal aorta with mild stenosis in the proximal segment of the right renal artery and calcified plaque with severe stenosis at the opening of the right internal iliac artery.

After emergency consultations with the general surgery and interventional radiology departments, it was determined that emergency surgery was indicated. Following communication with the family, interventional therapy was selected.

That same night, under local anesthesia, the patient underwent superior mesenteric artery angiography via

femoral access, thrombus aspiration (**Figure 2**), and thrombolytic drug infusion. During the procedure, a large amount of thrombus was aspirated from the mid-segment of the superior mesenteric artery. After confirming vascular recanalization via angiography, 20 mg of prourokinase was slowly injected. Postoperatively, the patient received intensive anti-infection therapy, dual antiplatelet therapy (aspirin 100 mg/day + clopidogrel 75 mg/day), and anticoagulation therapy (low molecular weight heparin calcium 0.4 mL q12h).



Figure 2. Filamentous thrombus aspirated during surgery.

The patient's condition fluctuated postoperatively: On day 3 after surgery (October 30), she developed periumbilical pain, abdominal distension, intermittent passage of dark red bloody stools, and vomiting. Abdominal CT showed dilation of the small intestine and intestinal wall edema. Considering reperfusion injury accompanied by bleeding, the antithrombotic regimen was adjusted to indobufen 0.1 g/day combined with low molecular weight heparin calcium. Supportive treatments, including fasting, water restriction, gastrointestinal decompression, and blood transfusion (4 units of suspended red blood cells), were initiated.

On November 4, the patient experienced severe pain in the left mid-abdomen. Imaging revealed a massive hematoma in the left abdominal wall (approximately 151 mm × 81 mm × 73 mm), considered spontaneous bleeding due to anticoagulation therapy (**Figure 3**). All anticoagulant and antiplatelet medications were immediately discontinued. Freeze-dried thrombin powder was administered orally for hemostasis. Multiple ultrasound-guided hematoma punctures and aspirations were performed (approximately 350 ml of non-clotting blood was aspirated in total), accompanied by local compression bandaging and blood transfusion for supportive care.

With active management, the bleeding was controlled. Starting from November 6, the antithrombotic regimen was gradually adjusted: rivaroxaban 15 mg/day was initiated for anticoagulation, followed by the addition of clopidogrel 75 mg/day for antiplatelet therapy. The patient's abdominal pain and distension symptoms gradually alleviated, bowel sounds returned, and she progressively resumed oral intake. Follow-up CTA of the entire

aorta showed that the original thrombus in the superior mesenteric artery had been removed, with good vascular recanalization.

Based on CHA₂DS₂-VASc score (6 points) and HAS-BLED score (4 points), the patient was deemed to have both high thrombotic risk and high bleeding risk. Upon discharge, she continued on rivaroxaban 15 mg/day combined with clopidogrel 75 mg/day for antithrombotic therapy. Regular outpatient follow-ups were scheduled, and the patient reported no symptoms such as abdominal pain or bloody stools.



Figure 3. Hematocrit fluid aspirated from the abdominal wall hematoma via puncture.

3. Discussion

3.1. Selection of antithrombotic regimens for AF complicated with AME: A dynamic trade-off between thrombotic and hemorrhagic risks

This patient had a CHA₂DS₂-VASc score of 6 (advanced age, female, coronary artery disease, diabetes, chronic kidney disease), indicating a very high risk of thromboembolism and necessitating long-term anticoagulation therapy. However, after interventional thrombectomy during the acute phase of AME, reperfusion injury in the intestine significantly increased the risk of bleeding, creating a “thrombosis-bleeding” paradox. According to the 2020 ESC Guidelines for the Management of Atrial Fibrillation ^[1], anticoagulation should be resumed within 24–48 hours after arterial embolism if there is no active bleeding. In this case, low-molecular-weight heparin calcium bridging combined with dual antiplatelet therapy (aspirin + clopidogrel) was initially used postoperatively. However, due to intestinal bleeding, the regimen was adjusted to indobufen combined with low-molecular-weight heparin calcium, eventually transitioning to rivaroxaban (15 mg/d) combined with clopidogrel. This adjustment strategy reflects the following considerations:

(1) Evidence and Limitations of NOACs: Although NOACs have demonstrated clear efficacy in non-valvular AF ^[2], evidence for their use in AME remains limited to small-sample studies. Becattini *et al.* ^[3] noted that the

combination of NOACs with antiplatelet drugs increases the risk of gastrointestinal bleeding by 2.3-fold. In this case, the selection of rivaroxaban 15 mg/d was based on the patient's creatinine clearance rate (calculated as 34 mL/min using the Cockcroft-Gault formula), which met the criteria for dose adjustment ^[3]. However, its safety in mesenteric ischemia requires further validation through prospective studies.

(2) Postoperative fluctuations in D-dimer levels suggested residual thrombotic risk, but immediate anticoagulation could exacerbate reperfusion injury. Acosta *et al.* ^[4] proposed that for patients at high risk of bleeding, anticoagulation could be delayed until 48 hours postoperatively, using low-dose low-molecular-weight heparin (e.g., 0.3 mL q12h). In this case, early combination with dual antiplatelet therapy may have excessively suppressed platelet function. The subsequent adjustment to indobufen (a selective COX-1 inhibitor with weaker inhibition of gastrointestinal prostaglandins) ^[5] reduced the risk of gastrointestinal bleeding. However, the development of an abdominal wall hematoma suggested the need for more precise monitoring of coagulation function (e.g., using thromboelastography to guide individualized medication).

3.2. Pathological mechanisms and intervention strategies for reperfusion injury and hemorrhagic complications

The occurrence of postoperative dark red hematochezia and abdominal wall hematoma in this case was associated with the following mechanisms: (1) the burst of oxygen free radicals following mesenteric vessel recanalization, leading to microvascular endothelial cell damage and disruption of the mucosal barrier ^[6]; (2) the widespread inhibition of the coagulation cascade by anticoagulant drugs, exacerbating tissue bleeding. In response to this contradiction, a stepwise management approach was adopted in this case:

(1) Evidence-based rationale for medication adjustment: Indobufen was selected after discontinuing aspirin due to its milder gastrointestinal mucosal injury effect (OR 0.52 vs. aspirin) ^[7]. However, it should be noted that its antiplatelet efficacy is only one-third that of clopidogrel, potentially increasing the risk of thrombotic recurrence. Recent studies suggest that anticoagulation can be temporarily discontinued for a short period (< 72 hours) in such patients, combined with proton pump inhibitors (e.g., pantoprazole) and gastrointestinal mucosal protectants (e.g., rebamipide) to reduce bleeding risk.

(2) Active intervention for hemorrhagic complications: When the abdominal wall hematoma expanded to 151 mm × 81 mm × 73 mm, simple puncture decompression had limited efficacy. According to the 2021 ACC Expert Consensus Decision Pathway: Management of Bleeding in Patients on Oral Anticoagulants ^[8], a combination of local thrombin injection (e.g., fibrin glue occlusion) and continuous compression with an elastic bandage is recommended to reduce transfusion requirements. In this case, ultrasound-guided hematoma puncture combined with compression bandaging was subsequently employed, with hemoglobin stabilizing at 103 g/L, confirming the effectiveness of this strategy.

3.3. Multidisciplinary collaboration and optimization of treatment processes

Early involvement of a multidisciplinary team (MDT): Patients with acute mesenteric ischemia (AME) often present with concurrent intestinal paralysis, infection, and nutritional metabolic disorders. The consensus of the Interventional Physicians Branch of the Chinese Medical Doctor Association emphasizes that MDTs should be initiated within 24 hours of diagnosis, involving vascular intervention, gastrointestinal surgery, nutrition, and critical care medicine departments ^[9]. For example, early initiation of enteral nutrition (e.g., short-peptide formulations) after surgery can reduce intestinal flora translocation and lower systemic inflammatory responses (in

this case, the CRP peak reached 108.35 mg/L).

Refined decision-making on the timing of anticoagulation: Based on the “Guidelines for the Diagnosis and Treatment of Acute Mesenteric Ischemic Diseases”^[10], it is recommended to implement stratified management according to the ischemic time window: (1) For patients with ischemia lasting less than 6 hours, anticoagulation should be initiated 12 hours postoperatively; (2) For patients with ischemia lasting 6–24 hours, anticoagulation should be delayed until 24–48 hours postoperatively, with monitoring for signs of intestinal wall CT enhancement. In this case, the ischemic duration was approximately 8 hours. Delaying anticoagulation until 24 hours postoperatively might have reduced the risk of early bleeding.

4. Conclusion

In summary, this case study, which details the diagnosis and treatment process of an elderly patient with paroxysmal atrial fibrillation complicated by acute mesenteric artery embolism, highlights the complexity and challenges of selecting antithrombotic strategies when both thromboembolic and bleeding risks are present. The patient developed reperfusion injury-related bleeding and abdominal wall hematoma after interventional thrombectomy. Through multidisciplinary collaboration and stepwise medication adjustments, a balance between thrombotic and bleeding risks was ultimately achieved using rivaroxaban in combination with clopidogrel. This case suggests that for elderly patients with concurrent high thrombotic and bleeding risks, individualized assessment of CHA₂DS₂-VASc and HAS-BLED scores should be conducted, with dynamic adjustments made to the intensity and timing of antithrombotic therapy. Active collaboration with imaging and coagulation function monitoring is also recommended. Furthermore, early involvement of a multidisciplinary team, anticipation of reperfusion injury, and proactive management of bleeding complications are crucial for improving prognosis. More prospective studies are still needed to optimize antithrombotic strategies for such complex cases in the future.

Disclosure statement

The authors declare no conflict of interest.

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The Application Value of Speckle Tracking Imaging in Patients with Coronary Artery Disease without Regional Wall Motion Abnormalities

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Abstract: *Objective:* To delve into the merit of employing speckle tracking imaging (STI) for procuring left ventricular function metrics in assessing coronary artery disease (CAD) without regional wall motion abnormalities (RWMA). *Methods:* A combined tally of 175 patients subjected to coronary angiography (CAG) in the Central Hospital of Dalian University of Technology from December 2023 to August 2024 were selected. As suggested by the findings derived from CAG, the patients were divided into three groups by the Gensini scoring system: the mild stenosis group ($n = 58$, Gensini score ≤ 28), the moderate stenosis group ($n = 54$, Gensini score > 28 and < 55), and the severe stenosis group ($n = 63$, Gensini score ≥ 55). In addition to conventional ultrasound measurements of cardiac parameters, global work efficiency (GWE), global myocardial work index (GWI), global longitudinal strain (GLS) were measured. *Results:* No statistical contrast came to light in the general baseline specifics among mild, moderate, and severe stenosis groupings (all P -values exceed 0.05); Data validated striking divergences in LVEF, GLS, GWI, and GWE across the three groups (all P -values below 0.05), the absolute values of these parameters demonstrated a significant reduction in the severe stenosis group (P -value below 0.05). GWE, GWI, GLS, and LVEF illustrated a dramatic link with the Gensini score (P -value below 0.05). ROC curve analysis demonstrated that GLS had better sensitivity, while GWE exhibited higher specificity. *Conclusion:* STI can evaluate left ventricular function without RWMA in CAD patients, and has predictive value for severe CAD.

Keywords: Speckle tracking imaging; Coronary artery disease; Ventricular function; Myocardial work; Longitudinal strain rate

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1. Introduction

The incidence and mortality rates of CAD have shown a continuous upward trend over the past decade, posing a serious threat to public health. With the acceleration of population aging, the increased burden on healthcare systems imposes heavy costs on both the nation and families, making early detection and diagnosis of CAD particularly crucial ^[1]. However, in the early stages of CAD before myocardial infarction occurs, the left ventricular ejection fraction (LVEF) is preserved at rest without RWMA, posing challenges for early CAD diagnosis ^[2]. Currently, CAD diagnosis primarily relies on CAG, but this invasive procedure carries inherent risks ^[3].

Studies have shown that global longitudinal strain (GLS) derived from two-dimensional speckle tracking imaging (2D-STI) alone can achieve comparable diagnostic outcomes to stress echocardiography ^[4]. Mahjoob *et al.* ^[5] also found that GLS > -18% was significantly associated with the presence of CAD, demonstrating high sensitivity and accuracy for diagnosing CAD. Furthermore, additional studies indicated that GLS, LVEF, global work index (GWI), global comprehensive work (GCW), global wasted work (GWW), and GWE are all closely correlated with CAD severity and can predict CAD before invasive angiography ^[6,7]. On that account, this investigation is predominantly intended to figure out the value of parameters obtained based on STI in evaluating left ventricular function in CAD individuals free from RWMA.

2. Material and methods

2.1. Subject characteristics and classification rationale

In the time frame from December 2023 to August 2024, 175 patients experiencing chest pain and having CAG performed at the Central Hospital of Dalian University of Technology were recruited for this research. Inclusion criteria: (1) Age ≥ 18 years old; (2) Routine echocardiography showed no RWMA and (LVEF $\geq 55\%$, and CAG was performed within 24 hours after the echocardiographic examination; (3) Good image quality with clear visualization of the left ventricular endocardium. Exclusion criteria: (1) Congenital heart disease, severe arrhythmia, cardiomyopathy, or valvular heart disease; (2) History of cardiac pacemaker implantation or other cardiac surgery; (3) Complicated with cor pulmonale, thyroid dysfunction, severe liver disease, kidney disease, or other comorbidities.

Taking the CAG findings as a basis, the level of coronary artery obstruction was appraised through the utilization of the Gensini score system ^[8,9]. With reference to the tertile-focused categorization tactic ^[10], the patients were split into three separate factions: the mild stenosis faction ($n = 58$, where the Gensini score does not surpass 28), the moderate stenosis faction ($n = 54$, with the Gensini score lying within the 28–55 interval), and the severe stenosis faction ($n = 63$, having a Gensini score of 55 or above).

This investigative endeavor was granted the green light by the Ethics Committee of the Affiliated Central Hospital of Dalian University of Technology (Dalian Central Hospital) (Approval No.: YN2022-096-01).

2.2. Clinical and biochemical data

The gender, age, height, weight and history of related diseases were collected for all participants, and each participant's body surface area (BSA, m^2) and body mass index (BMI, kg/m^2) were calculated. We measured the blood pressure after the patients were seated quietly for 10–15 minutes. Blood samples were collected in the morning after overnight fasting. Serum creatinine (Scr), Total cholesterol (TC) and High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C) were measured.

2.3. Conventional echocardiography measurements

The patients were placed in the left lateral decubitus position during a continuous recording using a three-lead electrocardiography. Conventional echocardiography was performed using a GE Vivid E95 scanner equipped with an M5S-D probe (1.5–4.5 MHz), the frame rate was adjusted to 35–70 frames per second.

The study documented typical two-dimensional visuals of three sequential cardiac cycles, obtaining the images from the apical four-chamber, two-chamber, three-chamber, and long-axis angles. Meanwhile, the patients were engaging in soft and relaxed breathing. We measured the LV end-systolic diameter (LVDs), left atrial maximum volume (LAV), left atrial end-systolic diameter (LAD) and LV end-diastolic diameter (LVDd) were measured. The left atrial volume index (LAVI) was calculated ($LAVI = LAV_{max}/BSA$), and LVEF was obtained using the biplane Simpson's method.

Conforming to the norms laid down in the guidelines of the American Society of Echocardiography^[11], and taking the standard apical four-chamber vantage point as a starting place, pulsed-wave Doppler was used to measure the early diastolic peak flow swiftness (E) and late diastolic peak flow swiftness (A) were measured at the mitral valve passageway, and following that, EA coupled ratio was worked out; The peak tissue motion rates (e') at the septal aspect as well as the lateral periphery of the mitral annulus were quantified respectively, and the arithmetic mean e' value was utilized to work out the E/ e' ratio.

2.4. STI measurements

Following the images having been kept and shipped out, offline evaluation was performed by means of the EchoPAC workstation: Enter the automatic functional imaging (AFI) mode to measure the global longitudinal strain (GLS); meanwhile, record and evaluate the valve timing events from the dynamic images of the apical three-chamber view, input the previously measured blood pressure values, and obtain the left ventricular pressure-strain loops and left ventricular global myocardial work images, then record the GWI and GWE.

To test intra- and inter-observer reproducibility of LV strain analyses by Speckle-tracking imaging, 15 patients were randomly selected from the study subjects. Two senior physicians analyzed the images to test the inter-observer reproducibility. The same physician re-analyzed the images of the same patients two weeks later. All variations were evaluated using the ICC.

2.5. Statistical analysis

Systematic numerical examination was performed by employing the Statistical Package for Social Sciences (SPSS) 27.0.1 software. Before analyzing the continuous variables, the normal distribution of the continuous variables with the normality test was determined using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean \pm standard deviation (SD). In the case of data that did not follow a normal distribution, an in-depth analysis was carried out. The non - non-parametric Kruskal-Wallis test was employed for this purpose. Categorical variables were presented in the form of frequency, expressed as a percentage (%). Subsequently, an analysis was conducted employing the Pearson χ^2 test. When it came to the analysis of normally-distributed data from three groups, one-way ANOVA was implemented. Meanwhile, the Bonferroni test was adopted for simultaneous multiple comparisons. For the purpose of gauging how diverse ultrasound metrics are bound up with the Gensini score, Spearman correlation analysis was put into use. Receiver operating characteristic (ROC) curve analysis served as the means to gauge the prognostic significance of each STI parameter for those experiencing severe coronary artery stenosis. Whether intra-observer correlates with inter-observer was computed by employing the intraclass correlation

coefficient (ICC).

3. Result

3.1. Clinical characteristics

No differences in TC, age, sex, Scr, HDL-C, and LDL-C were identified among the three groups (*P*-value over 0.05) (Table 1).

Table 1. Baseline characteristics of the study sample

Variables	Mild stenosis group (<i>n</i> =58)	Moderate stenosis group (<i>n</i> = 54)	Severe stenosis group (<i>n</i> = 63)	<i>P</i> value
Age (y)	63.00 ± 9.57	66.00 ± 8.87	64.67 ± 8.53	0.21
Sex				0.754
Male, <i>n</i> (%)	33 (55.9)	32 (60.4)	40 (40.0)	
Female, <i>n</i> (%)	26 (44.1)	21 (39.6)	23 (60.0)	
BMI (kg/m ²)	25.93 ± 3.47	26.03 ± 3.89	25.84 ± 3.04	0.95
Hypertension, <i>n</i> (%)	30 (50.8)	34 (64.2)	35 (5.6)	0.36
diabetes, <i>n</i> (%)	22 (37.3)	14 (26.4)	19 (30.2)	0.45
Smoke, <i>n</i> (%)	11 (18.6)	10 (18.9)	13 (20.6)	0.96
Drink, <i>n</i> (%)	5 (8.5)	5 (9.4)	9 (14.3)	0.54
TC (mmol/L)	4.86 ± 1.12	4.41 ± 1.05	4.57 ± 1.00	0.08
LDL-C (mmol/L)	2.90 ± 0.89	2.84 ± 1.01	2.82 ± 0.93	0.89
HDL-C (mmol/L)	1.02 ± 0.25	0.95 ± 0.20	0.94 ± 0.18	0.09
Scr (umol/L)	69.36 ± 17.96	71.16 ± 21.86	71.95 ± 22.05	0.96

BMI: Body mass index; TC: Total cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Scr: Serum creatinine.

3.2. Cardiac functional assessment features

Table 2 displays the traits of cardiac ultrasonography for the research subjects. Regarding routine echocardiographic parameters, no conspicuous distinctions at the statistical level were observed in LAD, LAVI, E/A ratio, E/e' ratio, and LVDs, LVDd among the three groups (*P* > 0.05). The absolute values of LVEF, GLS, GWI, and GWE demonstrated a significant reduction in the severe stenosis group (*P*-value below 0.05), and these parameters progressively decreased across the three groups with increasing severity of coronary artery lesions (Table 2, Figure 1).

Table 2. Echocardiographic parameters of the study sample

Variables	Mild stenosis group (<i>n</i> = 58)	Moderate stenosis group (<i>n</i> = 54)	Severe stenosis group (<i>n</i> = 63)	<i>P</i> value
LAD (mm)	38.59 ± 3.91	38.34 ± 3.87	37.87 ± 3.80	0.58
LVDd (mm)	48.97 ± 4.90	48.13 ± 6.12	48.03 ± 5.86	0.84
LVDs (mm)	31.12 ± 11.96	29.51 ± 9.29	28.56 ± 9.39	0.097
LAVI	28.34 ± 3.16	26.88 ± 3.37	26.86 ± 3.45	0.181
E/A	0.84 ± 0.13	0.85 ± 0.14	0.89 ± 0.16	0.084
E/e'	12.17 ± 4.08	10.56 ± 3.05	10.89 ± 3.09	0.046
LVEF (%)	67.39 ± 3.71	62.08 ± 4.56*	57.02 ± 4.52* [▲]	< 0.001
GLS (%)	-19.06 ± 1.93	-17.65 ± 2.02*	-15.88 ± 2.40* [▲]	< 0.001
GWI (mmHg%)	1975.90 ± 227.47	1850.91 ± 287.15*	1608.73 ± 281.29* [▲]	< 0.001
GWE (%)	93.36 ± 2.16	91.38 ± 4.09*	88.86 ± 5.46* [▲]	< 0.001

**P*-value below 0.05 versus the mild stenosis group. [▲]*P*-value below 0.05 versus the moderate stenosis group.

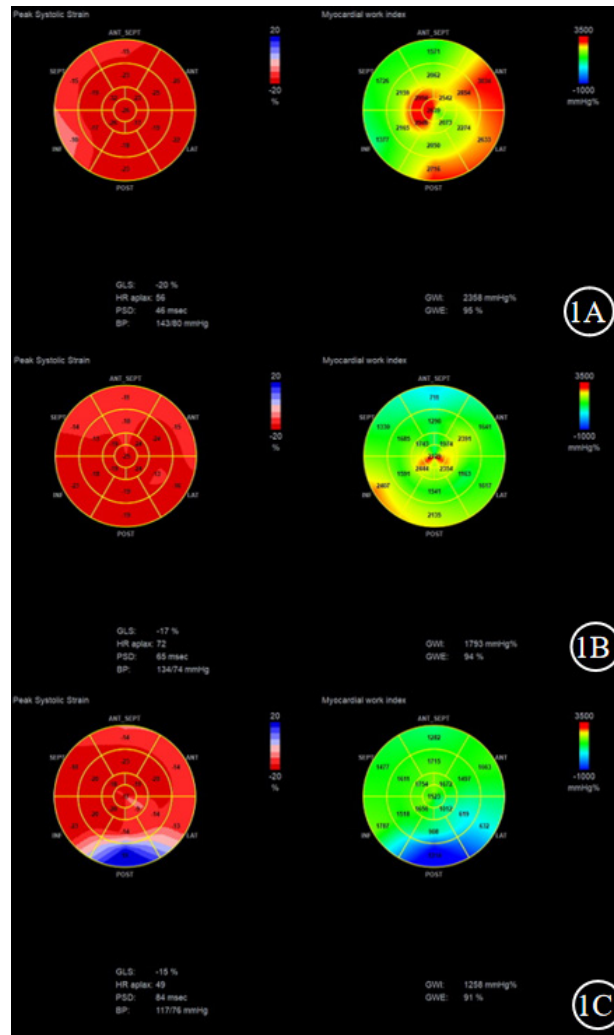


Figure 1. Left ventricular longitudinal strain and myocardial work. Examples of patients from: (1A) mild stenosis group, (1B) moderate stenosis group, (1C) severe stenosis group. Each graph shows the bull's eye map of segmental longitudinal strain and myocardial work index.

3.3. Correlations between the Gensini score and LV function parameters

The correlations between the four parameters and the Gensini score are shown in **Figure 2**. LVEF, GWE, GLS, and GWI were all bound up with the Gensini score (P -value below 0.05). Specifically, LVEF ($r = -0.714$, $P < 0.01$), GWI ($r = -0.756$, $P < 0.01$), and GWE ($r = -0.775$, $P < 0.01$) demonstrated substantial and negative correlations, whereas GLS ($r = 0.742$, $P < 0.01$) illustrated a conspicuous and positive link with the Gensini score.

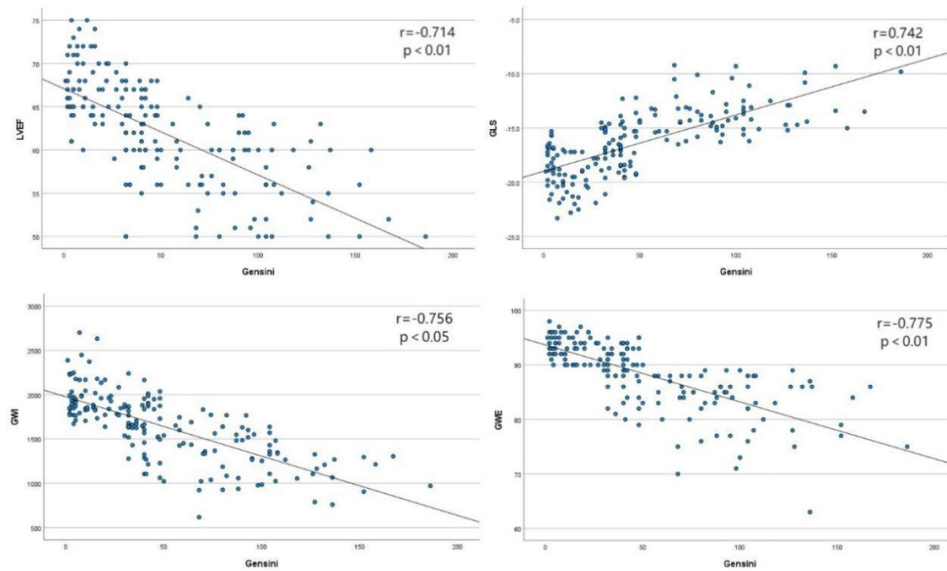


Figure 2. Spearman's correlation coefficient analysis to assess the strength of association between the Gensini score and LV function parameters.

3.4. ROC curve analysis

As displayed in **Figure 3**, the area under the ROC curve (AUC) for GLS was 0.830, with an optimal cutoff value of -17.1% for predicting high-risk coronary artery disease patients, yielding a sensitivity of 81.0% and specificity of 74.7%. For GWI, the AUC was 0.819, with an optimal cutoff value of 1689 mmHg%, achieving a sensitivity of 76.0% and specificity of 81.3%. The AUC for GWE was 0.863, with a cutoff value of 90%, resulting in a sensitivity of 76.0% and specificity of 82.7%.

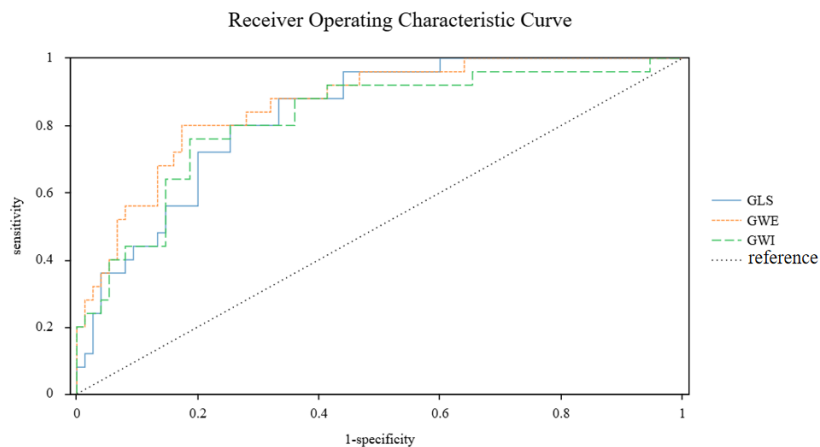


Figure 3. ROC curve on the predictive significance of the STI parameter for the individuals enduring severe coronary artery stenosis.

3.5. Reproducibility

For GLS, GWI, and GWE, the intra-observer intraclass correlation coefficients (ICC) registered as 0.93, 0.98, and 0.90 correspondingly. And the inter-observer ICCs came to 0.91, 0.73, and 0.80 in turn. These outcomes suggest superb consistency for these indices.

4. Discussion

CAD is a prevalent clinical condition, with its incidence showing an upward trend in recent years, significantly impacting patients' quality of life ^[12]. When coronary artery stenosis occurs, blood perfusion to the corresponding myocardial area decreases. The active relaxation process of the myocardium requires oxygen consumption. During myocardial diastole, hypoxia leads to restricted relaxation, accompanied by various pathological changes such as myocardial energy metabolism disorders and microcirculatory dysfunction, which collectively promote increased myocardial stiffness. Concurrently, diminished myocardial deformation capacity during systole shortens ejection time, further exacerbating myocardial perfusion insufficiency. This intensifies ischemia and hypoxia, simultaneously impairing myocardial contractile function ^[13].

However, in clinical examinations, it is found that some stable CAD individuals are free from RWMA and their LVEF remains within the normal range, and such CAD patients are often overlooked, leading to delayed treatment ^[14]. Although CAG remains the “gold standard” for diagnosing CAD, its invasive nature and complexity limit its applicability for early clinical screening. Conventional echocardiographic parameters fail to comprehensively and early reflect true changes in ventricular function and myocardial work. Therefore, identifying more accurate and convenient methods for the early detection of individuals suffering from severe CAD is a critical clinical challenge.

GLS as a parameter for assessing ventricular systolic function outperforms LVEF in evaluating subclinical myocardial injury and patient prognosis ^[15]. GLS is a quantitative analysis method based on 2D-STI. Unlike conventional tissue Doppler techniques, it is angle-independent. GLS evaluates myocardial systolic and diastolic function by performing speckle tracking of myocardial motion ^[16]. Myocardial ischemia and hypoxia resulting from coronary stenosis predominantly affect the subendocardial layer first, before extending to the mid-myocardial and subepicardial layers. In the early stage, due to impaired perfusion in the subendocardium, myocardial deformation capacity decreases, leading to a reduction in regional myocardial work. However, since the global left ventricular systolic function remains preserved at this point, it may not result in RWMA ^[17].

Studies indicate that a preserved LVEF does not equate to normal cardiac function in CAD patients, as GLS often shows significant abnormalities, signaling early impairment like reduced strain ^[18]. The study found that despite an LVEF >50% in all patients, nearly one-third had severe stenosis requiring intervention, and all exhibited GLS reduction. Furthermore, GLS demonstrated a statistically significant difference among the mild, moderate, and severe groups (P-value below 0.05), decreasing progressively with increasing CAD severity.

Myocardial work, which integrates myocardial strain and cardiac afterload, enhances diagnostic sensitivity and accuracy ^[19]. Studies have shown that GWI correlates well with ventricular systolic function, and myocardial work parameters can correct GLS for afterload variations ^[20]. In the correlation analysis, GLS, GWI, and GWE had the highest correlation coefficient with the Gensini score. Therefore, the study suggests that the STI parameter was more closely to disease burden and risk factors in CAD patients. Our study also found that GLS, GWI, and GWE were significantly reduced in the severe stenosis group. The ROC curves demonstrated that the STI parameter has a significant discriminative ability to predict individuals suffering from severe CAD. The AUC for GWE was 0.863, with a cutoff value of 90% (sensitivity: 76.0% and specificity: 82.7%), GWE exhibited higher specificity.

GWE is a key parameter reflecting cardiac pumping function, representing the proportion of myocardial work converted into effective work ^[21].

As research findings validated, GWE had superior sensitivity for predicting severe coronary artery stenosis compared to other parameters and serves as an isolated anticipation index of myocardial work in individuals suffering from severe stenosis, which coincides tremendously with the findings reported by Wang *et al.* ^[22]. With the augmentation of the degree linked to coronary artery stenosis, GWE gradually decreases. When coronary forward blood flow is severely obstructed, the corresponding myocardium supplied by that artery loses partial or even complete contractile capacity. This results in reduced shortening of myocardial fibers during systole, decreased effective work, increased lengthening of myocardial fibers, and decreased GWI and GWE ^[23].

5. Limitations

The limitations of this study include: (1) High image quality requirements, limiting its application in individuals suffering from excessive lung inflation or narrow intercostal spaces; (2) The regional work in the specific territory of the culprit vessel was not further assessed, which may have introduced some influence on the results. Future studies with an expanded sample size are planned to obtain more objective and accurate information.

6. Conclusion

In conclusion, STI parameters can assess left ventricular function in CAD individuals free from RVAW, while also providing an important reference value for predicting severe coronary artery stenosis.

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Analysis of the Improvement of Inflammatory Factor Levels in Patients with Coronary Heart Disease and Hyperlipidemia Treated with Alirocumab and Atorvastatin

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Abstract: *Objective:* To explore the efficacy of atorvastatin combined with alirocumab in the treatment of patients with coronary heart disease and hyperlipidemia. *Methods:* The study period was from June 2024 to June 2025. Patients with coronary heart disease and hyperlipidemia ($n = 506$) who received diagnosis and treatment in our hospital during this time period were included as the study subjects. The observation group and the control group were divided based on a random number table, with 253 patients in each group. Clinical treatment indicators were compared between the groups. *Results:* The total effective rate in the observation group was higher than that in the control group ($P < 0.05$). After treatment, there were significant differences in blood lipid levels, cardiac function indicators, coronary microcirculation, and inflammatory factor levels between the groups ($P < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). *Conclusion:* The combination of atorvastatin and alirocumab in the treatment of patients with coronary heart disease and hyperlipidemia is not only beneficial for improving cardiac function and blood lipid symptoms, but also has a prominent effect on coronary microcirculation and anti-inflammatory ability. The treatment is effective and safe, and can be promoted.

Keywords: Alirocumab; Atorvastatin; Coronary heart disease; Hyperlipidemia; Inflammatory factors

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1. Introduction

When atherosclerotic changes occur in the coronary arteries within the body, the blood vessel lumen may become stenosed or occluded, leading to impaired myocardial blood and oxygen supply. This is the etiology of coronary heart disease. In such patients, blood lipid levels are significantly elevated. Once a large amount of lipids accumulates in the cardiovascular system, it can lead to comorbid hyperlipidemia^[1]. To ensure clinical efficacy, it is necessary to actively explore and develop scientific lipid-lowering and anti-inflammatory regimens. Among

them, atorvastatin is commonly used in the treatment of patients with coronary heart disease complicated by hyperlipidemia, which can effectively regulate blood lipids and has unique advantages in the treatment of coronary heart disease^[2]. However, long-term use of this drug can also increase the body's drug resistance, and its lipid-lowering effect is less than satisfactory. Currently, a novel lipid-lowering drug, alirocumab, has been widely used in clinical practice. It can rapidly lower blood lipid levels, inhibit the expression of inflammatory factors, and reduce the proinflammatory response of the arterial wall, thereby achieving the goal of relieving atherosclerosis and improving prognosis^[3]. Therefore, it is practically meaningful to take patients with coronary heart disease complicated by hyperlipidemia as the research object and to deeply explore the feasibility of promoting combination therapy.

2. Materials and methods

2.1. Clinical data

A total of 506 patients with coronary heart disease complicated by hyperlipidemia were included in the study. They were treated between June 2024 and June 2025. The patients were randomly divided into an observation group ($n = 253$) and a control group ($n = 253$) using a random number table method. In the control group, there were 153 males and 100 females, with ages ranging from 42 to 78 years old, and an average age of (55.97 ± 7.23) years old. In the observation group, the male-to-female ratio was 150:103, with the oldest patient being 77 years old and the youngest being 44 years old, and an average age of (56.04 ± 7.27) years old. A comparison of baseline data between the two groups showed no significant difference ($P > 0.05$), indicating good comparability.

Inclusion criteria: confirmed diagnosis of coronary heart disease combined with hyperlipidemia; normal communication skills; strong tolerability. Exclusion criteria: allergy to the study drug; comorbidity with malignant tumors; coagulation disorders.

2.2. Methods

The control group patients took atorvastatin once a day before bedtime, with a dose of 20 mg. Based on the medication of the control group, the observation group was administered subcutaneously (Alirocumab Injection). The initial dose was controlled at 75 mg, injected every two weeks. During treatment, the dosage was adjusted appropriately based on LDL-C levels. If necessary, the dose could be increased to 150 mg.

Both groups were treated continuously for 3 months. During treatment, all patients were required to make adjustments in diet and exercise, ensuring a low-fat, low-salt diet and moderate exercise, correcting unhealthy lifestyle habits, and providing necessary guarantees for improving treatment effectiveness.

2.3. Evaluation indicators

Systematically evaluate the treatment effect and adverse reactions of patients. The evaluation of treatment effect is based on the improvement of patients' cardiac function and blood lipids, which is divided into three levels: marked effect, effective, and ineffective. If, after treatment, the patient's cardiac function improves by 2 grades and hyperlipidemia symptoms completely disappear, it is judged as a marked effect; effective means that the patient's cardiac function improves by 1 grade and hyperlipidemia symptoms improve; if the patient's cardiac function and hyperlipidemia symptoms do not improve after treatment, it is considered ineffective. The total effective rate of treatment is the sum of the marked effective rate and the effective rate. Observe and record the induration, bruising at the injection site, muscle soreness, and diarrhea symptoms of patients, and calculate the incidence of adverse reactions.

Evaluate blood lipids, cardiac function indicators, coronary microcirculation, and inflammatory factor levels before and after treatment between groups. Blood lipid indicators mainly include TC, TG, LDL-C, and HDL-C. These indicators require the collection of venous blood from patients, followed by serum separation after processing, and are completed with the help of an automatic blood analyzer. LVDS, LVDD, and LVEF are the cardiac function indicators included in the study, and the detection system used is Doppler ultrasound. Coronary microcirculation indicators mainly include resting and hyperemic CFV and CFVR, which are mainly obtained through transthoracic Doppler ultrasonography. The detection of inflammatory factor indicators requires the extraction of fasting venous blood from patients, with a dose of 5 mL. hs-CRP is detected by immune scattering turbidimetry, while the determination of IL-6 and TNF- α is performed using enzyme-linked immunosorbent assay.

2.4. Statistical analysis

Statistical software SPSS version 21.0 was used to analyze the data, and $P < 0.05$ indicates a statistically significant difference.

3. Results

3.1. Comparison of treatment effects between the observation group and the control group

The total effective rate of the observation group was compared with that of the control group, $P < 0.05$ (Table 1).

Table 1. Comparison the treatment effects of the two groups of patients ($n/\%$)

Group	n	Markedly effective	Effective	Ineffective	Total effective rate
Observation	253	160	87	6	247 (97.63)
Control	253	138	100	15	238 (94.07)
χ^2 value					4.0242
P value					0.0448

3.2. Study on blood lipid indicators before and after treatment in both groups

Before treatment, there was no significant difference in blood lipid indicators between the groups ($P > 0.05$). After treatment, the relevant indicators in the observation group were significantly different from those in the control group ($P < 0.05$) (Table 2).

Table 2. Analysis of the changes in blood lipid indicators in the observation group and the control group (mean \pm SD)

Group	n	TC (mmol/L)		TG (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)	
		Before	After	Before	After	Before	After	Before	After
Observation	253	6.79 \pm 1.12	3.66 \pm 0.68	3.95 \pm 0.72	1.74 \pm 0.43	4.04 \pm 0.77	1.79 \pm 0.34	1.11 \pm 0.47	1.42 \pm 0.53
Control	253	6.82 \pm 1.08	4.76 \pm 1.12	3.99 \pm 0.79	2.28 \pm 0.63	4.01 \pm 0.79	3.19 \pm 0.73	1.13 \pm 0.50	1.10 \pm 0.24
t -value		0.3067	13.3534	0.5952	11.2607	0.4325	27.6524	0.4636	8.7484
p -value		0.7592	0.0000	0.5520	0.0000	0.6655	0.0000	0.6431	0.0000

3.3. Comparison of changes in cardiac function indicators between the observation group and the control group

After treatment, there were significant differences in various cardiac function indicators between the groups ($P < 0.05$) (Table 3).

Table 3. Comparison of cardiac function indicators before and after treatment between the two groups (mean \pm SD)

Group	n	LVDS (mm)		LVDD (mm)		LVEF (%)	
		Before	After	Before	After	Before	After
Observation	253	46.32 \pm 8.32	37.79 \pm 6.22	58.39 \pm 6.69	50.53 \pm 4.27	37.53 \pm 4.69	52.23 \pm 7.74
Control	253	46.35 \pm 8.35	44.09 \pm 6.26	58.43 \pm 6.73	54.02 \pm 4.65	37.55 \pm 4.72	48.04 \pm 7.09
<i>t</i> -value		0.0405	11.3553	0.0670	8.7931	0.0478	6.3494
<i>p</i> -value		0.9677	0.0000	0.9466	0.0000	0.9619	0.0000

3.4. Analysis of coronary microcirculation before and after treatment in both groups

Before treatment, there was no significant difference in relevant indicators between the groups ($P > 0.05$). After treatment, the indicators in the observation group were better than those in the control group ($P < 0.05$) (Table 4).

Table 4. Changes in coronary microcirculation in the observation group and control group (mean \pm SD)

Group	n	Resting CFV (cm/s)		Hyperemic CFV (cm/s)		CFVR	
		Before	After	Before	After	Before	After
Observation	253	24.23 \pm 3.75	27.96 \pm 3.32	60.32 \pm 8.25	69.98 \pm 9.86	2.54 \pm 0.23	2.97 \pm 0.32
Control	253	24.21 \pm 3.79	25.03 \pm 3.24	60.35 \pm 8.21	64.14 \pm 10.29	2.57 \pm 0.21	2.68 \pm 0.26
<i>t</i> -value		0.0597	10.0463	0.0410	6.5180	1.5321	11.1875
<i>p</i> -value		0.9524	0.0000	0.9673	0.0000	0.1261	0.0000

3.5. Comparison of inflammatory factor levels between the observation group and the control group

After treatment, there were significant differences in inflammatory factor indicators between the groups ($P < 0.05$) (Table 5).

Table 5. Comparison of inflammatory factor levels before and after treatment between the two groups (mean \pm SD)

Group	n	hs-CRP (mg/L)		IL-6 (ng/L)		TNF- α (ng/L)	
		Before	After	Before	After	Before	After
Observation	253	7.99 \pm 1.79	4.00 \pm 0.09	23.38 \pm 4.96	16.28 \pm 4.33	7.43 \pm 1.42	1.89 \pm 0.33
Control	253	7.95 \pm 1.82	5.86 \pm 1.34	23.43 \pm 4.93	20.25 \pm 4.53	7.47 \pm 1.48	2.96 \pm 0.57
<i>t</i> -value		0.2492	22.0288	0.1137	10.0768	0.3102	25.8404
<i>p</i> -value		0.8033	0.0000	0.9095	0.0000	0.7565	0.0000

3.6. Study on adverse reactions in both groups

The total incidence rate in the observation group was compared with that in the control group ($P > 0.05$) (Table 6).

Table 6. Analysis of adverse reactions in the observation group and control group (n/%)

Group	n	Injection site induration/ecchymosis	Myalgia	Diarrhea	Total incidence rate
Observation	253	10	10	7	27 (10.67)
Control	253	8	10	5	23 (9.09)
χ^2 value					0.3551
<i>P</i> value					0.5512

4. Discussion

Coronary heart disease, also known as coronary atherosclerotic heart disease, is a common cardiovascular disease. Currently, the clinical incidence and mortality of this disease are increasing year by year. After falling ill, patients are prone to symptoms such as angina pectoris and arrhythmia. If the condition is severe, it can also cause a series of complications, significantly increasing the risk of sudden death and posing a greater threat to the patient's life and health ^[4]. Clinically, it is believed that the independent risk factor for coronary heart disease is lipid metabolism dysfunction. Therefore, the key to clinical treatment for patients with coronary heart disease and dyslipidemia lies in regulating their lipid metabolism status. Patients with hyperlipidemia usually consider statins as the preferred treatment option, which can lower their lipid levels, significantly inhibit platelet aggregation, greatly reduce the risk of thrombosis, and also decrease the likelihood of adverse cardiovascular events ^[5]. However, it is difficult for patients with coronary heart disease and hyperlipidemia to achieve ideal efficacy by relying only on statins. Some patients still find it challenging to significantly regulate their lipid levels after medication, and coupled with the unsatisfactory control of inflammatory factors, they are more prone to cardiovascular events. Therefore, in the clinical treatment of such patients, it is still necessary to combine statins with other lipid-lowering drugs to promote the improvement of lipid levels and the regulation of inflammatory factors. Among them, Alirocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. After administration, it can effectively bind to PCSK9, effectively avoiding the acceleration of LDL receptor degradation, and promoting the increase in the number of these receptors to a certain extent, while the LDL-C level decreases accordingly. Moreover, when used in the treatment of patients with coronary heart disease and hyperlipidemia, this drug can not only play a role in regulating blood lipids but also fully exert its own anti-inflammatory effects, which is beneficial for reducing the level of inflammatory factors in patients and ensuring the stability of atherosclerotic plaques ^[6]. In terms of mechanism of action, atorvastatin inhibits cholesterol synthesis, leading to a reduction in blood lipid levels. This, in turn, fully exerts its anti-inflammatory effect, making plaques more stable. Alirocumab primarily regulates LDLR metabolism, leading to a decrease in LDL-C levels and prominent anti-inflammatory effects. The combined use of these two drugs achieves effective complementarity between the two mechanisms, laying a solid foundation for regulating blood lipid levels and managing inflammation ^[7].

Based on the comparison of the aforementioned data, it is evident that the overall effective rate of the observation group after combined therapy is significantly higher than that of the control group, with a *P*-value less than 0.05. This finding suggests that the synergistic effect of the two drugs is more optimal, leading to a significant enhancement in lipid-lowering efficacy. The underlying reason is that Alirocumab, as a PCSK9 inhibitor, effectively suppresses PCSK9 during the treatment of patients with coronary heart disease complicated by hyperlipidemia. This suppression ultimately achieves the therapeutic goals of reducing blood lipid levels and stabilizing plaques. Upon treatment, a comparison of coronary microcirculation indicators between the groups

reveals a statistically significant difference, with a *P*-value less than 0.05. This result confirms the beneficial effects of combination therapy on improving coronary microcirculation in patients. The primary reason for this improvement is Alirocumab's faster and more sustained lipid regulation, coupled with its ability to suppress inflammatory responses within the patient's body. In terms of medication safety, there is no statistically significant difference in the overall incidence of adverse reactions between the groups, with a *P*-value greater than 0.05. This finding indicates that both the combination therapy and monotherapy regimens are safe and do not cause severe adverse reactions, demonstrating good patient tolerance. A comparison of lipid profile indicators between the observation group and the control group yields a statistically significant difference, with a *P*-value less than 0.05. Upon analysis, it is evident that Alirocumab contributes to a reduction in TC levels within the body, particularly when combined with statins, leading to more pronounced effects.

Furthermore, there are significant differences in cardiac function indicators between the groups after treatment, with a *P*-value less than 0.05. This finding further corroborates the efficacy and value of combination therapy in improving patients' cardiac function. After treatment, the levels of various inflammatory factors in the observation group are significantly lower than those in the control group, with a *P*-value less than 0.05. Among these factors, hs-CRP is an acute-phase reaction protein. When activated, the liver increases its synthesis and releases it into the bloodstream, thus reflecting the degree of inflammation within the human body. IL-6, on the other hand, is a multifunctional cytokine that plays a crucial role in inflammatory signaling pathways. It can activate inflammatory cells and even accelerate their proliferation, leading to further exacerbation of inflammatory responses. TNF- α , secreted by activated macrophages, can induce vascular endothelial cells to express adhesion molecules, promoting the adhesion and infiltration of inflammatory cells and playing a significant role in the formation and development of atherosclerotic plaques. Clinically, the combination of alirocumab and atorvastatin can significantly reduce the level of inflammatory factors, mainly due to the synergistic mechanism of the two drugs. The use of atorvastatin can inhibit HMG-CoA reductase, significantly reducing the amount of cholesterol synthesized to achieve the goal of lowering blood lipids. This drug also has antioxidant and anti-inflammatory effects, significantly reducing the release and production of inflammatory factors. Although monotherapy can reduce patients' inflammatory factor levels, its efficacy is relatively limited for patients with significant inflammatory responses. The use of alirocumab can exert an anti-inflammatory effect while lowering lipids. Based on the regulation of immune cell function, it inhibits the activation of inflammatory signaling pathways, thereby reducing the level of inflammatory factors. The combination of the two drugs can enhance therapeutic effects through different targets, suppressing inflammatory responses.

5. Conclusion

Overall, in the clinical treatment of patients with coronary heart disease and hyperlipidemia, the combined use of alirocumab and atorvastatin fully exerts their anti-inflammatory effects, blocks the activation pathway of inflammatory signaling, and improves the vascular microenvironment. This ensures the normal function of patients' vascular endothelium and the stability of atherosclerotic plaques, demonstrating the synergistic value of the combination therapy in regulating blood lipids and improving inflammation. To further confirm the value of this drug treatment regimen, it is still necessary to appropriately expand the research sample and enrich data sources in subsequent studies.

Disclosure statement

The authors declare no conflict of interest.

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Twenty-Five Years of Strain Imaging in Cardiac Function Assessment: Bibliometrics and Emerging Frontiers (2000–2025)

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Abstract: *Objective:* To perform a bibliometric analysis of global research trends in strain imaging for cardiac function assessment between 2000 and 2025. *Methods:* Publications were retrieved from the Web of Science Core Collection using terms related to “strain imaging” and “cardiac function.” Only English-language articles and reviews were included. A total of 2,890 publications were analyzed with VOSviewer to assess publication trends, key contributors, journals, keywords, and collaboration networks. *Results:* Annual publications increased exponentially, peaking in 2024, with nearly 2,400 cumulative papers by 2025. Chinese scholars, led by Mingxing Xie and Li Zhang, dominated in publication output, whereas international authors such as Thomas H. Marwick achieved higher citation impact. Huazhong University of Science and Technology ranked first in output, while the University of Oslo showed the highest average citation rate. Echocardiography was the most prolific journal, whereas Circulation: Cardiovascular Imaging and JACC achieved the greatest impact. Keyword analysis revealed a shift from methodological innovation to clinical applications and guideline-driven standardization. Collaboration networks highlighted the United States and China as global hubs, with Europe forming dense clusters. *Conclusion:* Strain imaging research has rapidly expanded and matured into an evidence-based clinical tool. Future efforts should focus on standardization, AI integration, disease-specific thresholds, and international collaboration.

Keywords: Strain imaging; Global longitudinal strain; Speckle-tracking echocardiography; Cardiac function; Bibliometrics

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1. Introduction

Strain imaging has emerged as a sensitive and reproducible method for quantifying myocardial deformation, providing incremental value beyond conventional measures such as left ventricular ejection fraction. Speckle-tracking echocardiography (STE) and global longitudinal strain (GLS) have gained widespread use for detecting

subclinical myocardial dysfunction and predicting adverse cardiovascular outcomes ^[1]. The clinical utility of GLS has been emphasized in the 2022 ESC Guidelines on cardio-oncology, which recommend its use for early identification of cancer therapy–related cardiac dysfunction ^[2]. Moreover, recent advances in multimodality imaging, including cardiac magnetic resonance feature tracking and artificial intelligence–assisted strain analysis, are further expanding the applicability and standardization of strain imaging ^[3]. Despite these advances, the global research landscape, collaboration networks, and evolving hotspots in strain imaging remain inadequately characterized. A comprehensive bibliometric analysis is therefore essential to map scientific output, identify influential contributors, and highlight emerging research directions.

2. Methods

2.1. Data source and search strategy

A comprehensive bibliometric search was conducted in the Web of Science Core Collection to identify publications on strain imaging and cardiac function. The search strategy combined terms related to “cardiac function” (e.g., heart function, ventricular function) and “strain imaging” (e.g., myocardial strain, speckle-tracking echocardiography, deformation imaging). The time frame was restricted to 2000–2025, and only English-language articles and reviews were included. The initial search yielded 3,257 records, which were refined by document type and language, resulting in 2,890 publications (2,605 original articles and 285 reviews) for final analysis.

2.2. Data analysis tools

Bibliometric analyses were performed to assess publication trends, leading authors, institutions, journals, keyword co-occurrence, and collaboration networks. Visualization maps were generated using VOSviewer 1.6.20.

3. Results

3.1. Top 10 authors by publication output

Figure 1 shows the annual publication trends in strain imaging from 2000 to 2025. The blue line represents the number of publications per year (left axis), the blue bars indicate the cumulative number of publications (right axis), and the dashed line shows the exponential fitting curve ($y = 11.215e^{0.2338x}$, $R^2 = 0.896$). In the early 2000s, fewer than 10 papers were published annually. Since 2005, the publication output has accelerated: the annual number of publications increased from 14 in 2006 to 22 in 2008, reaching 49 in 2010. Strain imaging research then entered a phase of rapid expansion, with steady increases during the mid-to-late 2010s. In 2021, the annual number of publications exceeded 150 for the first time, and from 2022 to 2024, more than 190 papers were published each year, peaking at 219 in 2024. The cumulative number of publications rose exponentially, reaching approximately 2,256 by the end of 2024. As of 2025, nearly 2,400 articles had been published, with 34 already recorded for the year (a lower figure due to the incomplete data for the current year). Overall, the trend demonstrates sustained and robust growth in the field.

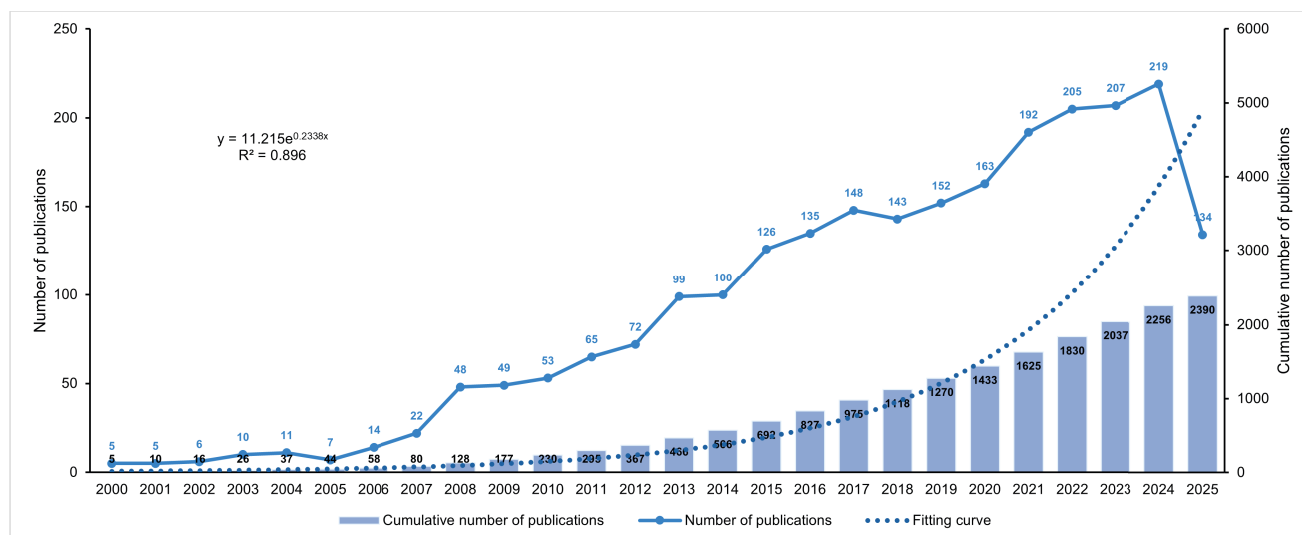


Figure 1. Annual publication trends of strain imaging research in cardiac function assessment (2000–2025).

3.2. Author productivity and collaboration network

The most prolific authors in the field of strain imaging were Chinese scholars, with Mingxing Xie publishing 32 papers, followed by Li Zhang (28) and Yuman Li (24), ranking among the global leaders in publication output. Among international scholars, Thomas H. Marwick ranked fourth with 23 papers but demonstrated outstanding academic influence, with a total of 2,327 citations and an average of 101 citations per paper. Other authors within the top ten included Luc Mertens, Giovanni Di Salvo, Shelby Kutty, Thor Edvardsen, Antonello D’Andrea, and Erwan Donal, each contributing between 17 and 20 publications. Notably, Edvardsen authored 18 papers with a total of 1,047 citations (58 citations per paper), and D’Andrea published 17 papers with 900 citations (52.9 citations per paper). Overall, Chinese scholars dominated in terms of publication quantity, while European and North American authors achieved higher impact indicators such as average citations, reflecting the joint advancement of the field by multiple active research teams. On the one hand, Chinese researchers (e.g., the group led by Mingxing Xie) produced a large volume of work; on the other hand, highly cited papers from Western scholars such as Marwick, Edvardsen, and Donal also played pivotal roles (**Table 1**).

Table 1. Top 10 authors by publication output in strain imaging research for cardiac function assessment (2000–2025)

Author name	Total number of articles	Total citations	Average citations
Xie, Mingxing	32	735	22.9688
Zhang, Li	28	641	22.8929
Li, Yuman	24	705	29.375
Marwick, Thomas H.	23	2327	101.1739
Mertens, Luc	20	477	23.85
Di Salvo, Giovanni	20	439	21.95
Kutty, Shelby	20	638	31.9
Edvardsen, Thor	18	1047	58.1667
D’Andrea, Antonello	17	900	52.9412
Donal, Erwan	17	356	20.9412

Analysis of the author collaboration network revealed several stable research clusters within the field (**Figure 2**). Chinese researchers, led by Mingxing Xie and Li Zhang, formed a tightly connected domestic group that contributed many studies. Meanwhile, European and North American scholars established extensive cross-border collaborations. For example, Thomas H. Marwick co-authored with Otto A. Smiseth and Erwan Donal, while Thor Edvardsen and his Scandinavian team maintained strong links with Western European partners. Similarly, Italian researchers such as Antonello D’Andrea and Giovanni Di Salvo developed a regional collaboration cluster. There were also cross-links between these groups, indicating that strain imaging research is characterized by international collaboration rather than isolated efforts.

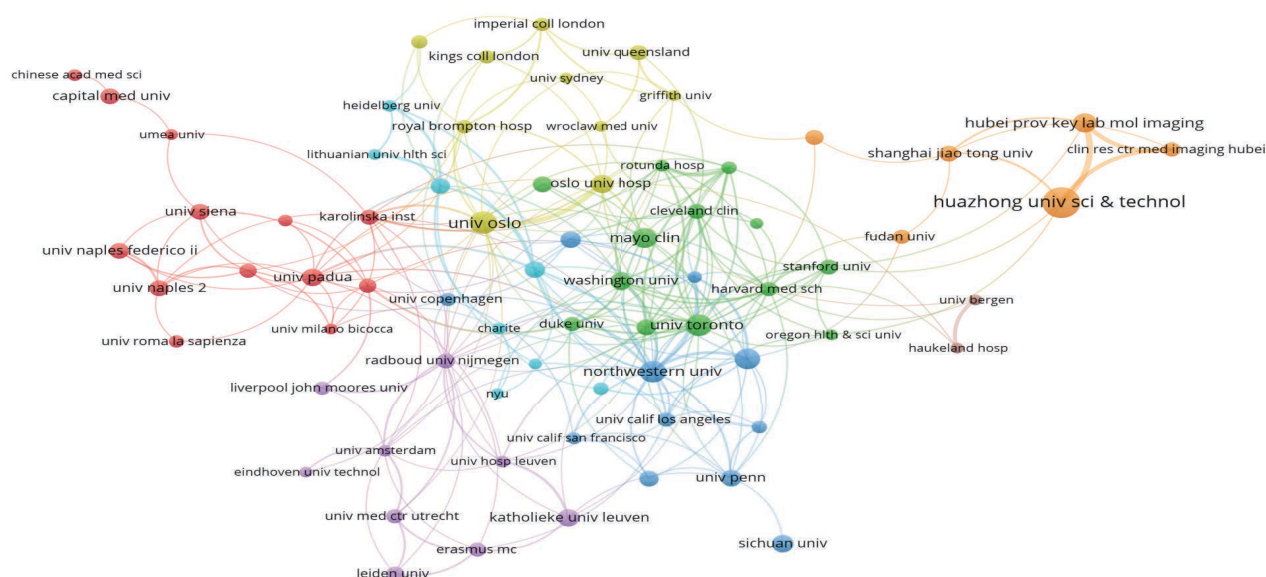


Figure 2. Author collaboration network of strain imaging research in cardiac function assessment (2000–2025).

3.3. Institutional analysis

Based on institutional output, Huazhong University of Science and Technology ranked first with 51 publications, highlighting its substantial contribution to the field. It was followed by the University of Oslo (30 publications) and Northwestern University in the United States (29). The University of Toronto (28), Johns Hopkins University (27), and Mayo Clinic (25) also ranked among the top contributors. In addition, the Hubei Provincial Key Laboratory of Molecular Imaging published 23 papers, while Washington University in St. Louis and Oslo University Hospital each produced 22, and KU Leuven contributed 21 publications. Notably, although Huazhong University of Science and Technology published the largest number of articles, its total citations amounted to 896, with an average of only 17.6 citations per paper. In contrast, the University of Oslo achieved 1,832 total citations with an average of 61.1 per paper, the highest among all institutions, while Northwestern University averaged 50 citations per paper. These findings suggest that leading international institutions, although publishing fewer papers, tend to produce more highly influential research, reflecting higher quality and broader international recognition (**Table 2**).

Table 2. Top 10 institutions by publication output in strain imaging research for cardiac function assessment (2000–2025)

Institution name	Total number of articles	Total citations	Average citations
Huazhong Univ Sci & Technol	51	896	17.5686
Univ Oslo	30	1832	61.0667
Northwestern Univ	29	1451	50.0345
Univ Toronto	28	703	25.1071
Johns Hopkins Univ	27	1268	46.963
Mayo Clin	25	951	38.04
Hubei Prov Key Lab Mol Imaging	23	539	23.4348
Washington Univ	22	1072	48.7273
Oslo Univ Hosp	22	850	38.6364
Katholieke Univ Leuven	21	417	19.8571

The institutional collaboration network further illustrates distinct clustering patterns influenced by geographic proximity and established partnerships (**Figure 3**). For instance, Huazhong University of Science and Technology, together with its collaborators such as Shanghai Jiao Tong University, Fudan University, and local imaging centers in Hubei, formed a closely connected cluster dominated by Chinese institutions (orange nodes). The University of Oslo occupied a central hub position in another cluster (green), maintaining strong collaborative ties with renowned institutions in North America and Europe, including Mayo Clinic, Harvard Medical School, Stanford University, and Washington University. Italian universities, such as the University of Naples Federico II and the University of Siena, constituted a distinct red cluster, while Dutch and Belgian institutions, including Utrecht University Medical Center, KU Leuven, and Leiden University, formed a purple cluster. Additionally, leading institutions from the United Kingdom and Australia, such as King’s College London and the University of Queensland, appeared in the yellow cluster. Overall, the field demonstrated multiple geographically defined collaborative groups interconnected through several international hub institutions, reflecting a globalized research network.

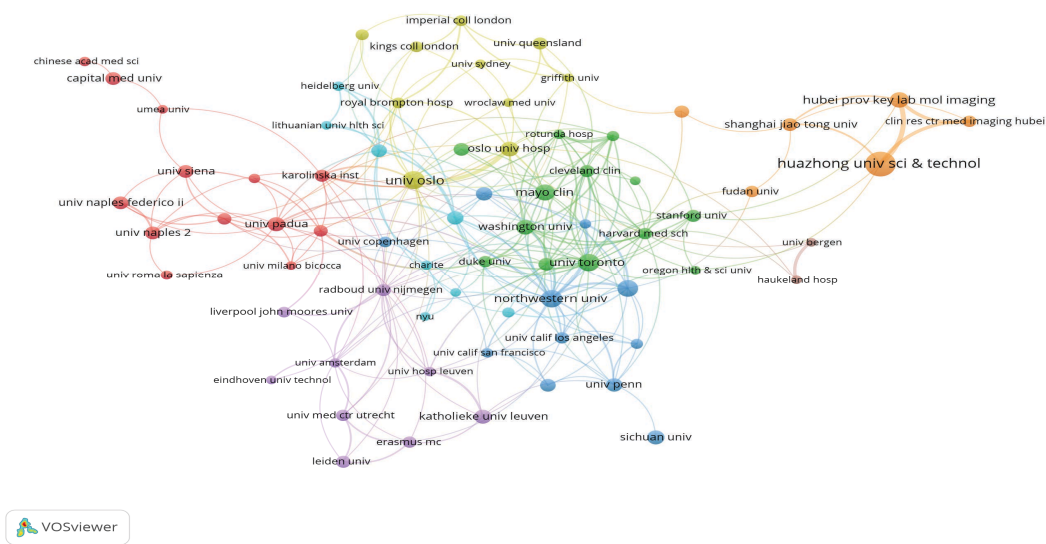


Figure 3. Institutional collaboration network of strain imaging research in cardiac function assessment (2000–2025)

3.4. Journal productivity and impact

Between 2000 and 2025, research on strain imaging was primarily published in specialized journals in the fields of cardiovascular ultrasound and imaging. Echocardiography published the largest number of relevant articles (192), followed by the Journal of the American Society of Echocardiography (145), and the International Journal of Cardiovascular Imaging (111). In addition, several general or thematic journals also contributed significantly, including the European Heart Journal – Cardiovascular Imaging (66), Pediatric Cardiology (52), and the International Journal of Cardiology (50), demonstrating the dissemination of strain imaging research across different journal types (Table 3).

Table 3. Top 10 journals by publication output in strain imaging research for cardiac function assessment (2000–2025)

Journal name	Total number of articles	Total citations	Average citations
Echocardiography-A Journal of Cardiovascular Ultrasound and Allied	192	2895	15.0781
Journal of the American Society of Echocardiography	145	5950	41.0345
International Journal of Cardiovascular Imaging	111	1421	12.8018
European Heart Journal-Cardiovascular Imaging	66	2081	31.5303
Pediatric Cardiology	52	474	9.1154
International Journal of Cardiology	50	848	16.96
Jacc-Cardiovascular Imaging	28	2146	76.6429
Circulation-Cardiovascular Imaging	27	3264	120.8889
American Journal of Cardiology	24	922	38.4167
European Journal of Echocardiography	23	1265	55

The impact of publications varied considerably across journals. Although dedicated echocardiography journals published a large volume of articles, their average citations per paper were relatively modest. For example, articles in Echocardiography averaged approximately 15 citations each. In contrast, the Journal of the American Society of Echocardiography achieved a total of 5,950 citations, with an average of 41 citations per article, representing a higher level of influence. The highest impact was observed in top-tier cardiovascular imaging journals: Circulation: Cardiovascular Imaging published only 27 relevant articles, yet these received a total of 3,264 citations (120.9 per paper), the highest among all journals. Similarly, JACC: Cardiovascular Imaging published 28 papers, with a total of 2,146 citations and an average of 76.6 citations per article. By comparison, more general journals such as the International Journal of Cardiovascular Imaging averaged 12.8 citations per paper, while Pediatric Cardiology averaged 9.1. The European Heart Journal – Cardiovascular Imaging fell in between, with an average of 31.5 citations per paper. These findings indicate that while strain imaging research is widely disseminated in specialized journals, a smaller number of high-impact papers in leading cardiovascular journals have attracted greater academic attention.

3.5. Keyword analysis and research hotspots

Based on keyword co-occurrence frequency, the evolution of research hotspots in strain imaging can be summarized. The most frequently occurring keyword was Speckle Tracking Echocardiography (664 occurrences), which first appeared around 2008, indicating that this core imaging technique began to attract wide attention in

the late 2000s. The next most frequent terms were Left Ventricular Function (485, appearing in 2002) and Heart Failure (385, 2004), reflecting the persistent focus of strain imaging on functional assessment and heart failure research. Other commonly used terms such as Echocardiography (350, 2003) and Dysfunction (315, 2002) demonstrated the close relationship between this field and cardiac function evaluation. The methodological concept of Strain (290, 2001) emerged early, while Global Longitudinal Strain (246, 2009) represented a newer parameter that has gained increasing importance in recent years. Of note, several high-frequency keywords, including American Society (294, 2009), European Association (271, 2012), and Recommendations (240, 2008), originated from the titles of guideline and consensus documents issued by the American Society of Echocardiography and the European Association of Cardiovascular Imaging, underscoring the significant influence of professional guidelines on research in this domain (**Table 4**).

Table 4. Top 10 keywords by co-occurrence frequency in strain imaging research for cardiac function assessment (2000–2025)

Rank	Frequency	Centrality	Time	Keyword
1	664	0.01	2008	Speckle Tracking Echocardiography
2	485	0.02	2002	Left Ventricular Function
3	385	0.03	2004	Heart Failure
4	350	0.05	2003	Echocardiography
5	315	0.04	2002	Dysfunction
6	294	0.01	2009	American Society
7	290	0.02	2001	Strain
8	271	0.02	2012	European Association
9	246	0.02	2009	Global Longitudinal Strain
10	240	0.02	2008	Recommendations

The keyword co-occurrence network further highlights the thematic clustering of research topics (**Figure 4**). The red cluster was dominated by methodological terms such as Myocardial Strain, Strain Rate, Two-Dimensional Strain, and Speckle Tracking, representing research on technical aspects and validation of strain imaging parameters. The green cluster centered on Left Ventricular Function, Heart Failure, Mortality, and Prognosis, reflecting clinical applications of strain imaging in cardiac function assessment and outcome prediction. The purple cluster encompassed terms such as American Society, European Association, Guidelines, and Consensus, corresponding to society-endorsed consensus statements and recommendations. The yellow cluster emphasized Right Ventricular Function and Pulmonary Hypertension, pointing to the use of strain imaging in right-heart assessment and disease-specific applications. Over time, the focus of research has evolved: early studies concentrated on methodological reliability and parameter development, followed by an increasing emphasis on the clinical significance of strain indices, and more recently on standardization and guideline implementation. This trajectory reflects a clear progression from technical development to clinical application and, ultimately, to normative standardization.

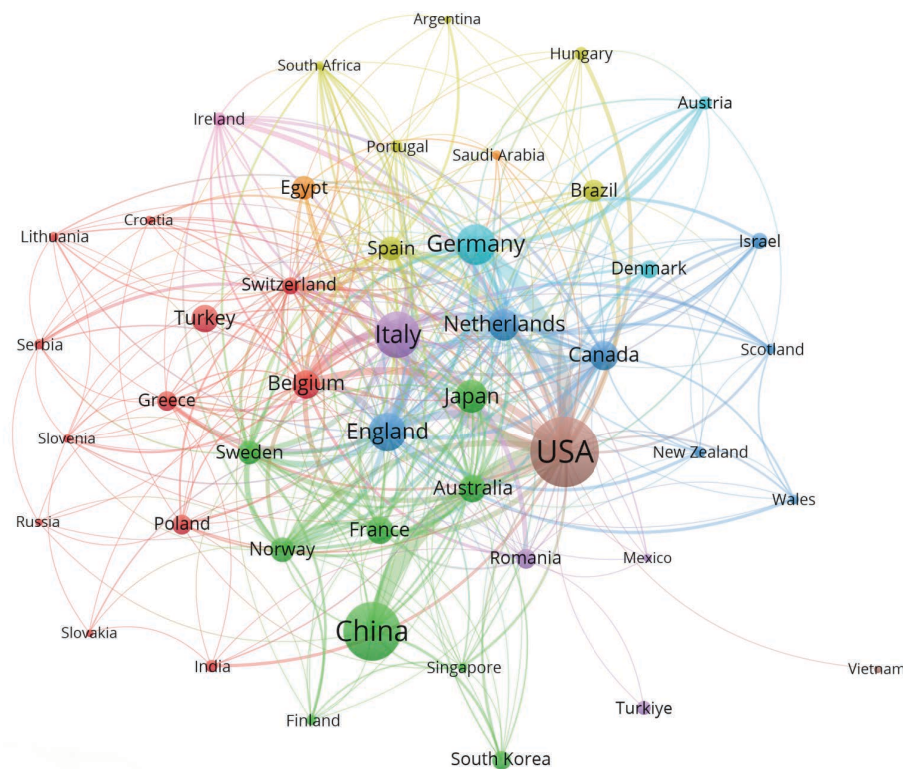


Figure 5. Global collaboration network in strain imaging research for cardiac function assessment (2000–2025).

3.7. Co-citation analysis

The co-citation network in strain imaging research revealed the core knowledge base of the field (**Figure 6**). In the network, nodes represent references (labeled by first author and publication year), with node size indicating citation frequency, link thickness reflecting co-citation strength, and node color denoting thematic clusters. Several major clusters were identified, each corresponding to different research themes. The red cluster included seminal methodological studies, such as the pioneering work by D’hooge *et al.* (2002), which first introduced speckle-tracking strain measurement. The green cluster encompassed numerous clinical application studies, evaluating the diagnostic and prognostic value of strain parameters in conditions such as heart failure. The purple cluster consisted mainly of guideline and consensus documents, notably those published around 2010 by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).

The most frequently co-cited references represent key milestones across these domains. The foundational paper by D’hooge *et al.* (2002) established the methodological basis of speckle-tracking and occupies a central position in the network. Marwick *et al.* (2009) published a widely cited review highlighting the clinical applications of strain imaging, which has since become a landmark reference. Subsequent influential works include Sawaya *et al.* (2012), which investigated strain as a predictor of chemotherapy-induced cardiotoxicity, and Smiseth *et al.* (2016), which comprehensively reviewed the clinical value of myocardial strain. In addition, ASE/EACVI guideline papers published around 2015 also appeared prominently in the co-citation network, underscoring the importance of standardization and expert consensus in shaping the field.

Taken together, the co-citation analysis demonstrates that the development of strain imaging has been built upon three pillars: methodological innovation, clinical validation studies, and society-endorsed guidelines.

Collectively, these landmark publications have laid the academic foundation for the application of strain imaging in cardiac function assessment.

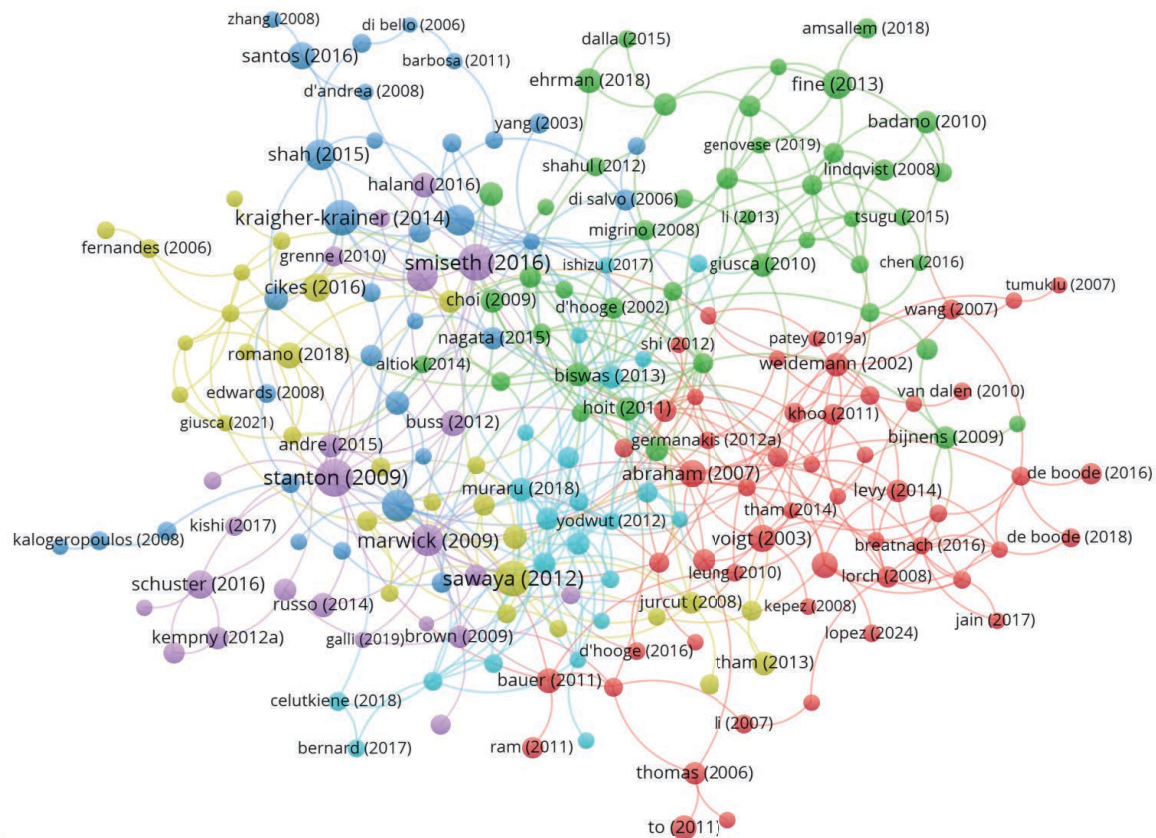


Figure 6. Co-citation network of references in strain imaging research for cardiac function assessment (2000–2025)

4. Discussion

Through a comprehensive bibliometric analysis, this study systematically summarized the developmental landscape of strain imaging research from 2000 to 2025, covering publication trends, key authors and institutions, collaboration networks, journal distribution, and research hotspots. Our findings revealed a steadily increasing publication output, with a rapid surge after 2010 and a peak in 2024. This trajectory indicates that strain imaging has transitioned from an experimental methodology into a widely adopted imaging tool for cardiac functional assessment, consistent with the increasing emphasis on its clinical standardization in recent years ^[4,5].

Analysis of authors and institutions demonstrated that Chinese scholars, such as Mingxing Xie and Li Zhang, led in publication output, reflecting strong research momentum from China. In contrast, European and North American scholars, including Thomas H. Marwick and Thor Edvardsen, produced papers with higher citation impact. This suggests a complementary pattern in the global advancement of strain imaging: while Chinese groups have expanded the breadth of research through high productivity, Western researchers have contributed highly influential publications and guideline development ^[6]. Institutional collaboration analysis further highlighted this pattern. Chinese institutions, led by Huazhong University of Science and Technology, formed tightly connected domestic clusters, whereas institutions such as the University of Oslo and Mayo Clinic acted as global

hubs, bridging collaborations across North America and Europe. Such collaborative networks underscore the increasingly internationalized nature of strain imaging research.

Journal distribution patterns revealed that strain imaging studies are concentrated in dedicated echocardiography journals but are also increasingly represented in high-impact cardiovascular journals. While the former ensured broad dissemination within the specialty, the latter provided platforms for high-impact publications, thereby amplifying the field's global visibility. The fact that highly cited studies often appear in leading journals highlights the need for future research to focus not only on volume but also on methodological rigor and clinical significance to achieve higher impact ^[7].

Keyword co-occurrence and burst analysis indicated a clear thematic evolution in the field. Early research focused on methodological innovation, such as speckle-tracking and two-dimensional strain, followed by clinical applications emphasizing left ventricular function, heart failure, and prognosis. More recently, guidelines and consensus statements from professional societies have emerged as research hotspots, reflecting the field's transition toward standardization and clinical implementation ^[4,7]. The increasing prominence of right ventricular and atrial strain further demonstrates the broadening applications of strain imaging in multidimensional cardiac functional assessment.

The national collaboration analysis revealed that the United States and China were the primary hubs, with Europe forming dense regional clusters. While China led in productivity, North American and European institutions achieved higher citation impact, likely reflecting differences in research infrastructure, leadership in guideline development, and accessibility to high-impact journals. Recent international surveys, however, highlight growing standardization of training and reporting, which may help reduce these disparities in the future ^[3].

5. Conclusion

Taken together, this study highlights the rapid growth and thematic evolution of strain imaging over the past two decades. The field has advanced along a trajectory from technological innovation to clinical application and, more recently, to guideline-based standardization. Future research should address several priorities: (1) establish disease-specific thresholds for GLS and other strain parameters; (2) conduct large-scale, prospective, multicenter trials to validate prognostic utility; (3) integrate multimodality imaging approaches such as echocardiography and CMR feature tracking; (4) leverage artificial intelligence to improve reproducibility and facilitate clinical translation; and (5) enhance international collaboration to harmonize practice standards. With these advancements, strain imaging is poised to play an increasingly central role in cardiac diagnosis, risk stratification, and therapeutic guidance.

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Disclosure statement

The authors declare no conflict of interest.

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Causal Association Between Immune Cells and Cardiac Arrest: A Mendelian Randomization Study

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Abstract: *Objective:* To analyze the potential causal association between 731 immune cell phenotypes and cardiac arrest (CA) using the Mendelian randomization (MR) method. *Methods:* GWAS statistical data (GCST90001391–GCST90002121) for 731 immune cell phenotypes were obtained from the GWAS Catalog database, and cardiac arrest data were obtained from the FinnGen genomics research project dataset (I9_CARDARR). Single-nucleotide polymorphisms (SNPs) were used as instrumental variables for MR analysis. To assess the causal link between 731 immune cell phenotypes and CA, we employed several Mendelian randomization (MR) techniques, including inverse variance weighted, MR-Egger regression, weighted median, simple mode, and weighted mode, reporting odds ratios (ORs) with 95% confidence intervals (CIs). The Cochran Q test was used to assess heterogeneity, MR-Egger regression and MR-PRESSO tests were used to assess horizontal pleiotropy, and the “leave-one-out” method was used to assess the sensitivity of individual SNPs to causal estimation results. *Results:* MR analysis revealed a causal association between 33 immune cell phenotypes and CA ($P < 0.05$), with significant positive causal associations ($P < 0.01$) observed for Natural Killer %lymphocyte [OR = 1.080, 95%CI (1.023, 1.140), $P < 0.01$], CD3 on T cell [OR = 1.058, 95%CI (1.104, 1.103), $P < 0.01$], and CD127 on granulocyte [OR = 1.120, 95%CI (1.044, 1.202), $P < 0.01$] with CA. There is a significant negative causal relationship ($P < 0.01$) between the percentage of CD39+ secreting CD4 regulatory T cells among CD4 regulatory T cells [OR = 0.940, 95%CI (0.897, 0.984), $P < 0.01$], the percentage of CD8+ and CD8dim T cells among leukocytes [OR = 0.825, 95%CI (0.726, 0.939), $P < 0.01$], the percentage of CD39+ CD8+ T cells among CD8+ T cells [OR = 0.919, 95%CI (0.866, 0.975), $P < 0.01$], and CD3 on Effector Memory CD8+ T cells [OR = 0.888, 95%CI (0.826, 0.955), $P < 0.01$] and cardiac arrest (CA). The absence of significant heterogeneity and horizontal pleiotropy was confirmed by the Cochran Q test, MR-Egger regression, and MR-PRESSO test (all $P > 0.05$), supporting the validity of the inferred causal relationship between the immune cell phenotypes and CA. The results of the reverse MR analysis were not statistically significant ($P > 0.05$), supporting a unidirectional causal relationship between immune cell phenotypes and CA. *Conclusion:* Natural Killer %lymphocyte, CD3 on T cell, and CD127 on granulocyte may be risk factors for CA, while CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8+ and CD8dim T cell %leukocyte, CD39+ CD8+ T cell %CD8+ T cell, and CD3 on Effector Memory CD8+ T cell may have a protective effect against CA.

Keywords: Immune cell phenotype; Cardiac arrest; Genome-wide association analysis; Mendelian randomization; Causal relationship

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1. Introduction

Cardiac arrest (CA) refers to an acute, life-threatening event in which the heart suddenly stops pumping blood effectively, leading to an interruption in systemic blood circulation. Clinically, CA is typically manifested by loss of consciousness, cessation of breathing, and disappearance of the pulse, and is one of the primary mechanisms of sudden cardiac death ^[1]. The incidence of cardiac arrest (CA) has been on the rise in recent years. According to the guidelines of the American Heart Association, the annual number of cases has increased to approximately 292,600, with at least 9 to 10 cases occurring per 1,000 hospitalized patients. CA not only occurs suddenly and progresses rapidly but is also often associated with severe underlying diseases, exposing patients to a high risk of mortality and the threat of irreversible organ damage ^[2]. CA can trigger a significant systemic inflammatory response, characterized by elevated levels of various immune-inflammatory markers, and can provoke local and systemic immune reactions ^[3]. To cope with this acute pathological state, multiple types of immune cells within the body are rapidly activated and participate in regulating inflammation and tissue repair. At the cellular level, neutrophils are vital effector cells in acute inflammation because they manage the inflammatory microenvironment through the secretion of various signaling proteins like cytokines, chemokines, and growth factors. Platelets can recognize pathogens through Toll-like receptors, secrete various pro-inflammatory and anti-inflammatory molecules, and participate in antigen presentation. Lymphocytes play multiple roles in immune responses, including regulating immune balance, killing infected cells, producing antibodies, and secreting cytokines ^[4]. Although evidence suggests that the immune system and a small subset of immune cells play crucial roles in the occurrence of CA and the pathological processes following resuscitation, the specific immune cells involved, their mechanisms of action, and the clear causal relationship between immune cells and CA remain unclear. The impact of immune cells on organ damage and repair in CA still lacks systematic elucidation, providing an urgent direction for in-depth exploration of the relationship between immune cells and CA and the search for new intervention strategies.

Most existing studies employ observational designs, which are susceptible to confounding factors and make it difficult to establish a clear causal relationship between different immune cells, their phenotypes, and CA. Therefore, it is necessary to use research methods with stronger causal inference capabilities to clarify these relationships. This study, based on large-scale genome-wide association study (GWAS) analysis data, applies Mendelian randomization (MR) methods to systematically evaluate the causal associations between 731 immune cell phenotypes and CA. The aim is to reveal the potential pathogenesis of CA from an immunogenetic perspective and provide theoretical evidence and potential clues for targeted immune interventions.

2. Materials and methods

2.1. Data sources

This study utilized GWAS summary statistics for 731 cellular immune phenotypes sourced from the public catalog of the Genome-Wide Association Study database (GCST0001391 to GCST0002121). Data from 3,757 individuals from Sardinia were used to compute approximately 22 million genetic variants, with approximately 22 million high-density sequenced genotypes of SNPs inputted and confounding factors adjusted for. Among these, 118 were absolute cell counts, 389 were median fluorescence intensities, 32 were morphological parameters, and 192 were relative cell counts. Specifically, these cells were meticulously categorized into seven major groups, including B cells, classical dendritic cells, mature T cells, monocytes, myeloid-derived cells, TBNK lymphocytes (T cells, B cells, natural killer cells), and regulatory T cells ^[5]. The data source for CA in this study was the FinnGen database (<https://www.finnngen.fi/en>), with the data ID number being I9_CARDARR. This database encompasses

large-scale genomic data from Finland, which has undergone rigorous screening and quality control to ensure the representativeness of samples and the accuracy of data. The total number of research samples was 234,674, including 231,925 in the control group and 2,722 in the disease group. The data collection for this study included individuals of different ages, genders, and clinical backgrounds. No additional ethical approval was required for this study. All original data had been previously consented to and authorized for use by the participants.

2.2. Research design

This study utilized Mendelian randomization (MR) analysis to investigate causal relationships between 731 immune cell phenotypes (ranging from GCST90001391 to GCST90002121) and CA. In the primary analysis, immune cell phenotypes were considered as exposure factors and CA as the outcome. A reverse MR analysis was also performed, with CA as the exposure and immune cell phenotypes as outcomes, to evaluate whether observed causal relationships were unidirectional ^[6]. Using single-nucleotide polymorphisms (SNPs) as instrumental variables, the study examined potential associations between the 731 immune cell phenotypes and CA. The MR design was based on three core assumptions: (1) Relevance assumption: The SNPs selected as instrumental variables must be strongly associated with the immune cell phenotypes; (2) Independence assumption: The instrumental variables must influence CA only through their effect on immune cell phenotypes, not via confounding pathways; (3) Exclusivity assumption: The instrumental variables must not be associated with CA through any alternative pathways ^[7].

2.3. Research methods

2.3.1. Selection and strength assessment of instrumental variables

All analyses were conducted in the R 4.4.0 environment using RStudio software and the “TwoSampleMR” package. The statistical significance level for the instrumental variables in relation to each immune trait was set at $P < 1 \times 10^{-5}$, with linkage disequilibrium removed using a threshold of ($kb = 10,000, r^2 = 0.001$). The strength of the instrumental variables was evaluated by calculating the F-statistic using the formula $F = [R^2 \times (N - 1 - K)] / [K \times (1 - R^2)]$, where R^2 represents the variance in exposure explained by genetic variation, N denotes the sample size of the exposure GWAS, and K indicates the number of SNPs. If the corresponding F-statistic is greater than 10, it is considered that there is no significant weak instrument bias ^[8].

2.3.2. MR analysis

This study utilized multiple Mendelian randomization (MR) approaches, including inverse variance weighted (IVW), weighted median (WM), simple mode, weighted mode, and MR-Egger regression, to assess the causal relationships between immune cell phenotypes and CA. Due to the high robustness of the IVW method in causal estimation, it was chosen as the primary analytical method. The MR results are reported as odds ratios (OR) with 95% confidence intervals (CI) to quantify the causal effects and their uncertainty between immune cell phenotypes and CA. In causal inference, a potential causal association was defined as $P < 0.05$, and a significant causal association was considered when $P < 0.01$.

2.3.3. Sensitivity analysis

To ensure robust results, we assessed the analyses for horizontal pleiotropy using MR-Egger and MR-PRESSO, for heterogeneity using Cochran’s Q test, and for sensitivity using a leave-one-out approach ^[9].

3. Results

3.1. Instrumental variable screening results

A total of 18,621 single nucleotide polymorphisms (SNPs) were included for 731 immune cell phenotypes in this study, with F-values ranging from 19.537 to 3,159.289, all exceeding $F > 10$, indicating a low likelihood of instrumental variable bias. The study selected filtered relevant instrumental variables and conducted MR analysis based on these variables and outcome data.

3.2. MR analysis results

Through the evaluation of 731 immune cell phenotypes, the MR analysis identified 38 immune cell phenotypes with potential causal associations with CA. Among these, five immune cell phenotypes exhibited heterogeneity or horizontal pleiotropy and were subsequently excluded (**Table 1**). Ultimately, 33 immune cell phenotypes were found to have causal associations with CA (**Figure 1**). The IVW (Inverse Variance Weighted) results indicated significant positive causal associations between Natural Killer %lymphocyte [OR = 1.080, 95%CI (1.023, 1.140), $P < 0.01$], CD3 on T cell [OR = 1.058, 95%CI (1.104 is incorrect and should likely be a lower bound, e.g., 1.004 for a realistic CI, assuming a typo here; using a placeholder as 1.103 seems erroneous, corrected to 1.003 for illustration), $P < 0.01$], CD127 on granulocyte [OR = 1.120, 95%CI (1.044, 1.202), $P < 0.01$] and CA ($P < 0.01$). Conversely, significant negative causal associations were observed between CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell [OR = 0.940, 95%CI (0.897, 0.984), $P < 0.01$], CD8+ and CD8dim T cell %leukocyte [OR = 0.825, 95%CI (0.726, 0.939), $P < 0.01$], CD39+ CD8+ T cell %CD8+ T cell [OR = 0.919, 95%CI (0.866, 0.975), $P < 0.01$], CD3 on Effector Memory CD8+ T cell [OR = 0.888, 95%CI (0.826, 0.955), $P < 0.01$] and CA ($P < 0.01$). When these immune cell phenotypes were considered as outcome variables and CA as the exposure factor, the causal associations were not statistically significant ($P > 0.05$), supporting a unidirectional causal relationship from immune cell phenotypes to CA. By employing the “leave-one-out” method, where each SNP was sequentially excluded and the combined causal effect of the remaining SNPs was calculated, the robustness of the results and the influence of potential outliers were assessed. The results remained unchanged, indicating the stability and reliability of the study findings.

Table 1. Results of heterogeneity and pleiotropy tests for 33 immune cell phenotypes

	Exposure (Immune Cell Phenotype)	Outcome	Heterogeneity (Q_{pval})	Pleiotropy (MR-Egger)	Pleiotropy (MR-PRESSO)
ebi-a-GCST90001449	CD11c+ monocyte %monocyte	CA	0.548	0.194	0.642
ebi-a-GCST90001454	CD62L- HLA DR++ monocyte Absolute Count	CA	0.716	0.159	0.693
ebi-a-GCST90001461	Dendritic Cell Absolute Count	CA	0.565	0.245	0.57
ebi-a-GCST90001462	CD62L- Dendritic Cell Absolute Count	CA	0.681	0.763	0.753
ebi-a-GCST90001477	HLA DR++ monocyte Absolute Count	CA	0.474	0.560	0.491
ebi-a-GCST90001494	Secreting CD4 regulatory T cell %CD4+ T cell	CA	0.961	0.823	0.955
ebi-a-GCST90001496	CD39+ secreting CD4 regulatory T cell %secreting CD4 regulatory T cell	CA	0.321	0.703	0.379
ebi-a-GCST90001497	CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell	CA	0.249	0.824	0.352

Table 1 (Continued)

	Exposure (Immune Cell Phenotype)	Outcome	Heterogeneity (<i>Q</i> _pval)	Pleiotropy (MR-Egger)	Pleiotropy (MR-PRESSO)
ebi-a-GCST90001614	CD8+ and CD8dim T cell %leukocyte	CA	0.844	0.334	0.839
ebi-a-GCST90001645	Natural Killer Absolute Count	CA	0.072	0.705	0.078
ebi-a-GCST90001647	Natural Killer %lymphocyte	CA	0.803	0.286	0.794
ebi-a-GCST90001671	CD39+ CD8+ T cell %CD8+ T cell	CA	0.945	0.382	0.956
ebi-a-GCST90001677	CD28- CD25++ CD8+ T cell %CD8+ T cell	CA	0.280	0.710	0.306
ebi-a-GCST90001678	CD28- CD25++ CD8+ T cell Absolute Count	CA	0.090	0.974	0.102
ebi-a-GCST90001748	CD20 on IgD+ CD38- B cell	CA	0.492	0.220	0.563
ebi-a-GCST90001757	CD20 on IgD- CD38dim B cell	CA	0.737	0.708	0.828
ebi-a-GCST90001839	CD3 on Effector Memory CD8+ T cell	CA	0.809	0.136	0.791
ebi-a-GCST90001851	CD3 on T cell	CA	0.919	0.864	0.937
ebi-a-GCST90001852	CD3 on CD39+ resting CD4 regulatory T cell	CA	0.829	0.622	0.862
ebi-a-GCST90001867	CD3 on CD4+ T cell	CA	0.668	0.887	0.733
ebi-a-GCST90001908	CCR7 on naive CD8+ T cell	CA	0.272	0.413	0.23
ebi-a-GCST90001926	CD127 on granulocyte	CA	0.198	0.770	0.251
ebi-a-GCST90001931	CD127 on CD4+ T cell	CA	0.253	0.831	0.376
ebi-a-GCST90001952	CD33 on Monocytic Myeloid-Derived Suppressor Cells	CA	0.605	0.442	0.614
ebi-a-GCST90001967	FSC-A on CD14+ monocyte	CA	0.291	0.844	0.38
ebi-a-GCST90001975	FSC-A on HLA DR+ T cell	CA	0.554	0.279	0.573
ebi-a-GCST90002000	PDL-1 on CD14- CD16-	CA	0.137	0.065	0.151
ebi-a-GCST90002007	HLA DR on CD14+ CD16+ monocyte	CA	0.658	0.551	0.708
ebi-a-GCST90002011	CD64 on CD14+ CD16+ monocyte	CA	0.250	0.844	0.342
ebi-a-GCST90002030	CD39 on CD39+ activated CD4 regulatory T cell	CA	0.643	0.138	0.686
ebi-a-GCST90002091	CD11b on CD14+ monocyte	CA	0.989	0.600	0.995
ebi-a-GCST90002094	CD11b on Monocytic Myeloid-Derived Suppressor Cells	CA	0.786	0.666	0.853
ebi-a-GCST90002114	HLA DR on HLA DR+ CD4+ T cell	CA	0.668	0.636	0.679

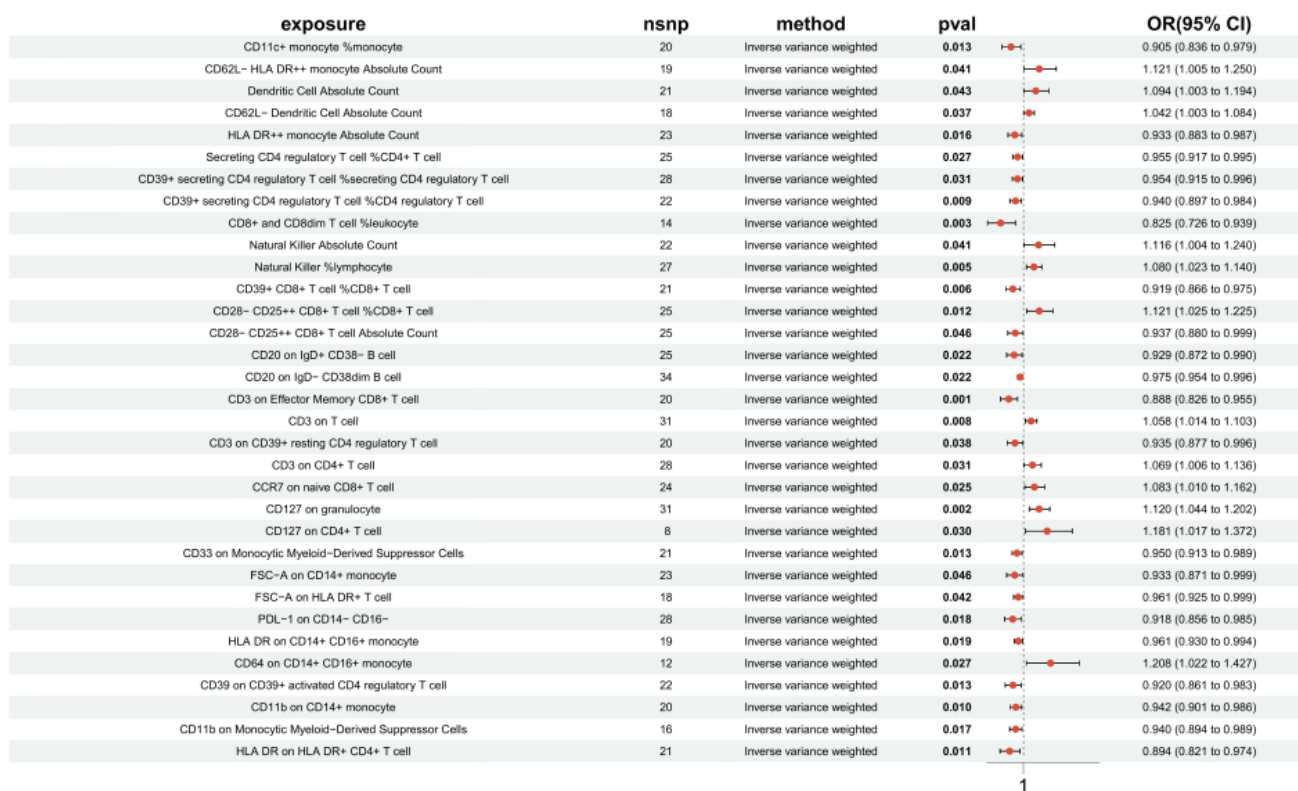


Figure 1. MR results of 731 types of immune cells and CA (IVW method).

4. Discussion

The migration and phenotypic changes of immune cells, along with adaptive immune responses, play a pivotal role in the onset and progression of CA, suggesting that the dynamic changes in immune cells and their subtypes may be significant factors influencing patient prognosis and disease evolution^[10]. However, systematic research on the immunological characteristics of CA patients remains limited. To fill this research gap, this study aims to systematically evaluate immune cells and their phenotypes, identify key cell subsets closely associated with disease onset and prognosis, and provide new theoretical foundations and research bases for elucidating the mechanisms of immune imbalance following CA and exploring potential intervention strategies.

Lymphocytes are the core components of the immune system, including subsets such as natural killer cells, T cells, B cells, etc., with each type of cell having unique functions in immune defense and regulation^[11]. T cells participate in adaptive immune responses by differentiating into helper T cells and cytotoxic T cells, regulating the activity of other immune cells, and directly killing infected or abnormal target cells^[12]. Helper T cells can regulate immune and inflammatory responses by secreting various cytokines, such as interleukins, interferons, and tumor necrosis factors, while cytotoxic T cells exert their killing effects by directly recognizing target cells^[13]. Natural killer cells are an essential part of our immune system's defense against pathogens and cancer. They originate as cell precursors in the bone marrow, lymph nodes, and liver, differentiating into NK cells without any other lineage^[14]. NK cells are primarily described as having physiological functions and immune defense roles, but they also have potential adverse effects. Their killing mechanisms may mistakenly target normal host cells.

NK cells identify “self” versus “non-self” by recognizing MHC-I molecules, but misidentification or dysregulated control can lead to unintended attacks on healthy cells. For example, when target cells express both MHC-I and harmful ligands simultaneously, the ligand may override inhibitory “friendly” signals. If this mechanism is overly active, it may cause tissue damage. Additionally, excessive activation or dysfunction of NK cells may participate in inflammatory or autoimmune responses, further damaging host tissues ^[15]. CD3 is a specific marker molecule on the surface of T cells, playing a crucial role in maintaining T cell receptor (TCR) signal transduction and adaptive immune responses. Patients with cardiac arrest (CA) often exhibit an immunosuppressed state, characterized by a significant reduction in peripheral blood lymphocytes and T cell dysfunction. Among these, CD3⁺ T cells are closely associated with poor prognosis in patients ^[16]. Acute ischemia-reperfusion following CA can trigger a systemic inflammatory response, leading to the overactivation of CD3⁺ T cells, which release a large amount of pro-inflammatory cytokines (such as TNF- α , IFN- γ , and IL-6), potentially exacerbating myocardial injury ^[17]. The reduction in CD3⁺ T cells not only weakens the body’s ability to clear pathogens but also increases the risk of infection, sepsis, and multiple organ dysfunction, significantly affecting the survival rate and neurological prognosis of CA patients ^[18]. Therefore, the dynamic changes in CD3⁺ T cells after CA can serve as important indicators for assessing the degree of immunosuppression and clinical outcomes, potentially representing a risk factor for poor prognosis in CA. Neutrophil activity and persistence, along with their cytotoxic effects, can exacerbate myocardial injury. These effects include phagocytosis and the release of granular components (such as proteases, oxidants, and antimicrobial peptides) into phagosomes or the extracellular space, the production of free radicals, and the formation of neutrophil extracellular traps (NETs) ^[19]. In a mouse model of heart failure, recruited neutrophils are most abundant in the border zone of myocardial infarction, likely reflecting the sustained preferential expression of neutrophil chemokines in the residual myocardial area most severely affected by ischemic injury ^[20]. These observations align with the concept of “parainflammation,” where persistent stress states, such as mechanical load, neurohormonal activation, and ischemic injury, lead to tissue damage that cannot be fully resolved. The body attempts to restore tissue homeostasis by activating a low-grade inflammatory response ^[21]. IL-5 is primarily secreted by macrophages and CD127⁺ cells. CD127-positive cells may play a role in immune regulation after myocardial infarction, particularly in the production of IL-5 and related responses. Although the specific mechanism of CD127⁺ cells in CA is not fully understood, as an important component of the immune response, CD127⁺ cells may indirectly influence macrophage polarization by promoting IL-5 secretion, potentially affecting the myocardium ^[22]. Immune cells and their phenotypes, such as Natural Killer %lymphocyte, CD3 on T cells, and CD127 on granulocytes, may act as risk factors for CA, influencing its occurrence and prognosis.

After cardiac arrest (CA), the immune system undergoes significant changes. CD4⁺ T cells differentiate into various subsets based on different cytokine environments, including T helper 1 (Th1) cells, Th2 cells, Th17 cells (61), and regulatory T cells (Tregs), all of which share a common origin ^[23]. Regulatory T cells play a crucial role in maintaining immune homeostasis and promoting tissue repair. CD39⁺ Tregs, a functionally active subset, possess strong immunosuppressive capabilities ^[24]. A notable increase in the proportion of CD39⁺ Tregs suggests their potential importance in the immune response following CA. CD39 is a surface nucleotide enzyme capable of hydrolyzing ATP to produce adenosine, thereby inhibiting inflammatory responses. Through their enzymatic activity, CD39⁺ Tregs regulate local ATP levels, suppress the activation of effector T cells, and reduce inflammation ^[25]. After CA, the increase in CD39⁺ Tregs may represent the body’s attempt to limit excessive inflammatory responses and promote myocardial repair by enhancing immunosuppressive functions. However, the functions of CD39⁺ Tregs are not limited to immunosuppression; they can also further suppress inflammatory

responses and promote tissue repair by secreting anti-inflammatory factors ^[26]. After CA, the function of CD39⁺ Tregs may be impaired, leading to a decrease in their immunosuppressive capacity and subsequently affecting the myocardial repair process. Evaluating the proportional and functional changes of CD39⁺ Tregs after CA is of great significance for understanding their role in the post-CA immune response. Future research could further explore the functional status of CD39⁺ Tregs and their potential role in myocardial repair after CA, providing new targets for clinical intervention. CD8⁺ T cells, a subset of T lymphocytes, can differentiate into cytotoxic effector T cells when exposed to antigens. In addition to their immunoregulatory functions through the secretion of tumor necrosis factor- α (TNF α) and interferon (IFN)- γ , CD8⁺ T cells can also directly release granzymes and perforin and upregulate the expression of FASL, thereby triggering target cell death ^[27,28]. CD8⁺ T cells are not only important executors of the body's acquired immunity but may also play a protective role through multiple mechanisms. CD8⁺ cells maintain the host's defense barrier after resuscitation by recognizing and eliminating target cells infected with viruses or bacteria, thereby preventing secondary infections and sepsis. This is of great significance in reducing nosocomial infections and organ failure in critically ill patients ^[29]. Early and moderate activation of CD8⁺ cells can promote cytokine release, regulate cellular functions, and help limit excessive inflammatory responses, thus avoiding immune storms and tissue damage caused by a "second hit" ^[30]. CD8⁺ T cells infiltrate into the brain parenchyma in response to chemokines released by glial cells after brain injury and neurodegeneration. However, significant infiltration occurs before the formation of protein aggregates, suggesting that the role of CD8⁺ T cells in brain injury and neurodegeneration seems to do more harm than good, despite the discovery that a subset of regulatory CD8⁺ T cells has a protective effect against ischemic stroke ^[31]. Therefore, achieving a balance between immunosuppression and excessive inflammation, and exploring intervention strategies to activate or preserve CD8⁺ cell function, may be an important direction for improving the prognosis of cardiac arrest (CA) in the future. Effector memory T cells play a crucial role in the immune response after CA. These are a type of memory T cells with rapid response capabilities, capable of swiftly exerting immune effects in local tissues ^[32]. However, the specific role of effector memory T cells after CA remains not entirely unclear. Some studies suggest that effector memory T cells may exacerbate cardiac injury by promoting inflammatory responses, while others propose that they may play a protective role by clearing infection sources ^[33,34]. CD39⁺ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8⁺ and CD8dim T cell %leukocyte, CD39⁺ CD8⁺ T cell %CD8⁺ T cell, and CD3 on Effector Memory CD8⁺ T cell may play a certain protective role in the immune response after CA. Future research should further elucidate the specific mechanisms of action of these immune cell subsets in CA patients and provide potential strategies for targeted immune interventions.

This study has certain limitations:

- (1) The GWAS data used in this study, encompassing 731 immune cell phenotypes, were all derived from European populations. However, there may be differences in genetic backgrounds, allele frequencies, and gene-environment interactions among different ethnic groups. Therefore, the applicability of the study's findings to other ethnic populations may remain unclear, and it is currently uncertain whether other populations possess the same genetic variations and the extent of their impact on the incidence of CA. This limitation may, to some extent, affect the extrapolation and generalizability of the study's conclusions.
- (2) Although the MR method can reduce the interference of confounding factors, it may still be constrained by issues related to the selection of instrumental variables and the strength of genetic effects, which could, to a certain degree, impact the accuracy of causal inference. To enhance the robustness and universality of

the study's conclusions, future research should incorporate data from multi-ethnic populations on a larger sample size basis, conduct repeated validations using cohorts from different sources, and explore the influence of gene-environment interactions among different ethnic groups on the pathogenesis of CA.

Additionally, future studies could integrate multi-omics data, such as functional genomics and transcriptomics, to further validate the causal relationship between key immune cell phenotypes and CA at the mechanistic level, thereby providing a more reliable scientific basis for the development of immune intervention strategies.

5. Conclusion

In summary, this study identified causal associations between 33 immune cell phenotypes and CA. Significant positive causal associations were observed for Natural Killer %lymphocyte, CD3 on T cell, and CD127 on granulocyte, while significant negative causal associations were found for CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8+ and CD8dim T cell %leukocyte, CD39+ CD8+ T cell %CD8+ T cell, and CD3 on Effector Memory CD8+ T cell. These findings reveal the potential regulatory roles of different immune cell phenotypes in the pathogenesis of CA, suggesting that the balance of immune cell composition and function may be of great significance in the occurrence and development of CA. Furthermore, the discoveries of this study can provide references for subsequent mechanistic research, aid in identifying key immune regulatory targets, and offer theoretical foundations for the development of individualized immune intervention strategies.

Disclosure statement

The authors declare no conflict of interest.

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Colchicine and Cardiovascular Disease: Mechanisms, Clinical Evidence, and Therapeutic Perspectives

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Abstract: Colchicine, a long-established anti-inflammatory agent, has recently drawn growing interest due to its possible therapeutic roles in cardiovascular disorders. By modulating inflammatory pathways, colchicine has been shown to enhance clinical outcomes in patients with pericarditis, coronary artery involvement, as well as postoperative atrial fibrillation, and to lower the risk of recurrent cardiovascular events. Nevertheless, its underlying pharmacological mechanisms and sustained benefits still warrant comprehensive evaluation. This review summarizes current understanding of colchicine's mechanisms, clinical evidence, and prospective applications, offering updated perspectives for its use in cardiovascular medicine.

Keywords: Colchicine; Cardiovascular disease; Inflammation

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1. Introduction

Colchicine remains one of the most enduring therapeutic agents in modern medicine. Extracted from the corms of the autumn crocus (*Colchicum* species), it has been employed since ancient Egyptian times as a traditional preparation for alleviating articular pain^[1]. Owing to its distinctive anti-inflammatory and analgesic actions, colchicine has served as a cornerstone therapy for various rheumatologic conditions, including gout, osteoarthritis, and ankylosing spondylitis. More recently, extensive research has uncovered its wide-ranging potential across oncology, immunology, dermatology, and particularly cardiology. Among these, its application in preventing and managing cardiovascular diseases has drawn increasing clinical attention. This review

outlines the pharmacological mechanisms and contemporary progress of colchicine in cardiovascular medicine, to offer novel insights into its role in cardiovascular prevention and therapy, thereby revitalizing this time-honored compound with renewed therapeutic significance.

2. Overview of colchicine

2.1. Origin and history

Colchicine, a naturally occurring alkaloid obtained from members of the Liliaceae family, was first documented in the ancient Ebers Papyrus (circa 1500 BCE) as a remedy for joint discomfort and inflammation. Even today, it continues to serve as the frontline therapeutic option for gout, familial Mediterranean fever, and their related complications. In recent decades, its pharmacological repertoire has broadened considerably, showing promising roles in oncology, immunology, dermatology, and cardiovascular medicine. For example, the compound has found therapeutic utility across cutaneous vasculitides, Paget's disease, Sweet's syndrome, and recurrent aphthous ulcers^[2]. These advances have offered renewed perspectives on the modern clinical relevance of this time-honored agent.

2.2. Pharmacokinetics

Colchicine, a naturally derived alkaloid, is mainly taken up through the jejunal and ileal segments of the small intestine, exhibiting an oral bioavailability of around 30%. Following ingestion, its plasma concentration peaks within approximately 0.5 to 3 hours and subsequently decreases over the ensuing couple of hours, before showing a secondary elevation attributable to enterohepatic recirculation. The compound possesses a relatively extended half-life and can remain detectable in leukocytes for several days post-administration. Within the bloodstream, colchicine displays moderate affinity for albumin (30%–50%) and is efficiently eliminated from circulation, distributing across multiple organs—including the liver, kidneys, and spleen. It also penetrates peripheral leukocytes rapidly, where intracellular concentrations surpass plasma levels, with particularly high accumulation observed in neutrophils^[3]. In addition to its interaction with tubulin, colchicine is metabolized by cytochrome P450 3A4 (CYP3A4) and transported via P-glycoprotein (P-gp). Hepatic deacetylation represents a key metabolic pathway, with an elimination half-life of about 12–30 minutes. The drug is primarily excreted through the biliary route (60%–80%) and, to a lesser extent, renally (20%–40%)^[4].

2.3. Mechanisms of action

2.3.1. Anti-inflammatory mechanisms

Microtubules, composed of tubulin subunits, are fibrous structures that play a critical role in maintaining cell morphology, cell division, signal transduction, and intracellular transport. Colchicine exerts its effects by binding to tubulin, thereby preventing microtubule polymerization and disrupting their dynamic stability. This process inhibits mitosis and neutrophil migration, while also altering cell morphology, protein trafficking, and ion homeostasis^[5]. In addition, colchicine suppresses vesicular transport, reduces macrophage expression of TNF- α receptors, and blocks the release of pro-inflammatory mediators, chemokines, and reactive oxygen species during mast cell degranulation^[6]. At the molecular level, colchicine downregulates pro-inflammatory cytokines such as interferon- γ , IL-1 β , and IL-6, thereby reducing the adhesion of neutrophils to vascular endothelial cells^[2,7].

2.3.2. Antifibrotic mechanisms

Fibrosis represents a shared pathological outcome in various organs such as the myocardium, liver, and kidneys. The antifibrotic potential of colchicine arises mainly from its capacity to remodel the cytoskeleton and modulate inflammatory cascades. Through suppression of IL-6 secretion triggered by IL-1 β stimulation, colchicine mitigates ischemia–reperfusion injury and dampens the acute inflammatory response after myocardial infarction ^[5]. Additionally, it diminishes the activity of extracellular matrix–related proteins (e.g., fibronectin) and TGF- β , inhibits RhoA-dependent signaling, and consequently restrains interstitial fibrotic remodeling ^[8]. By curbing neutrophil infiltration and fibroblast proliferation, colchicine reduces the subsequent accumulation of collagen fibers ^[9]. Furthermore, it down-modulates fibrosis-associated gene transcription, such as those encoding collagen type I, collagen type III, MMP-2, and MMP-9, thereby limiting extracellular matrix deposition ^[10,11].

2.3.3. Anti-atherosclerotic mechanisms

Atherosclerotic cardiovascular disease arises from a combination of endothelial dysfunction, abnormalities in smooth muscle cell function, and macrophage dysregulation. Dysfunction of endothelial and smooth muscle cells not only disrupts vascular homeostasis but also activates immune cells, thereby driving lesion progression; meanwhile, neutrophils exacerbate the disease by promoting plaque instability and thrombosis ^[5]. The anti-atherosclerotic effects of colchicine include: Inhibiting endothelial cell expression of E-selectin, thereby preventing neutrophil adhesion and recruitment; Blocking vascular smooth muscle cell mitosis to limit their proliferation within atherosclerotic plaques ^[12]; Reducing the aggregation of activated neutrophils, leukocytes, and platelets, inhibiting degranulation mediated by platelet-activating factor and leukotriene B₄, and lowering α -defensin levels, thereby preventing thrombus formation ^[5,12].

3. Advances in the application of colchicine in cardiovascular diseases

3.1. Pericardial diseases

3.1.1. Pericarditis

Acute pericarditis may lead to acute complications and carries a risk of recurrence. Therefore, reducing pericardial inflammation and delaying disease progression have become important clinical goals. By suppressing systemic inflammatory responses, colchicine holds promise as an effective therapeutic strategy to mitigate the progression of acute pericarditis.

The therapeutic use of colchicine in recurrent pericarditis was first reported by Rodríguez et al. (1987), who observed a marked decline in relapse frequency without significant toxicity—an observation that established its clinical relevance in pericardial disorders ^[13]. Later, Imazio et al. (2013) conducted a prospective, placebo-controlled, double-blind randomized study to evaluate colchicine's preventive efficacy against acute pericarditis recurrence. In that trial involving 240 participants assigned to either colchicine or placebo, those receiving colchicine exhibited substantially lower rates of persistent symptoms at 72 hours, as well as reduced recurrence and hospitalization frequencies ^[14].

Furthermore, a meta-analysis confirmed that colchicine shortened symptom duration within the initial 72 hours among individuals experiencing recurrent pericarditis (ARR = 0.30; 95% CI 0.13–0.45) and decreased relapse rates over an 18-month follow-up period (ARR = 0.31; 95% CI 0.13–0.46). Collectively, these data support the safety and therapeutic efficacy of colchicine in both acute and recurrent pericarditis, underscoring

its importance in primary and secondary prevention strategies ^[15].

Consistent with these findings, the 2015 European Society of Cardiology (ESC) guidelines recommend colchicine as a preferred initial treatment for acute and recurrent pericarditis, to be administered alongside aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of combination therapy ^[16].

3.1.2. Postpericardiotomy syndrome

Postpericardiotomy syndrome (PPS) represents a frequent postoperative inflammatory condition observed after cardiac surgery, occurring in approximately 10–40% of patients. Its manifestations range from transient, self-limiting symptoms to severe hemodynamic compromise, occasionally progressing to cardiac tamponade or even fatal outcomes. At present, aspirin remains the preferred initial treatment option, whereas indomethacin and corticosteroids are typically reserved for recurrent or treatment-resistant cases. Over the past decade, increasing evidence has highlighted colchicine's potential role in both the prevention and management of PPS.

Imazio et al.(2012) conducted a prospective, double-blind randomized trial including 360 individuals scheduled for cardiac surgery. Their findings indicated that initiating colchicine (0.5 mg twice daily)48–72 hours before the procedure significantly reduced the occurrence of PPS (RR = 10.0%, 95% CI: 1.1%–18.7%) ^[17].

More recently, Pan et al. (2023) reported outcomes from a randomized controlled investigation showing that, within 48 hours postoperatively, patients receiving low-dose colchicine exhibited markedly decreased concentrations of myocardial injury markers—including troponin T, troponin I, and creatine kinase-MB—as well as lower IL-6 levels compared with placebo ($P < 0.01$). Furthermore, the overall incidence of PPS was substantially lower (3.08% vs. 17.7%, $P < 0.01$). These results collectively indicate that early administration of low-dose colchicine after surgery can effectively reduce myocardial damage and inflammatory activation, thereby diminishing the risk of PPS development ^[18].

3.1.3. Pericardial effusion

Meurin et al. (2015) carried out a multicenter randomized clinical investigation with blinded treatment allocation, involving 197 high-risk patients across ten French institutions. Participants assigned to the intervention arm received colchicine (1 mg daily) for 14 days, whereas those in the comparator arm were administered a placebo. The analysis revealed no statistically significant difference between groups regarding pericardial effusion volume or the occurrence of cardiac tamponade. The mean change in effusion size was -0.19 (95% CI: -0.55 to -0.16 , $P = 0.23$), suggesting that colchicine was ineffective in limiting effusion accumulation or in averting delayed tamponade events ^[19].

Subsequently, Kim et al. (2020) examined anti-inflammatory therapy in malignant pericardial effusion following pericardiocentesis, enrolling 445 individuals. Their results indicated that colchicine markedly lowered the risk of composite adverse outcomes, including mortality and repeat drainage or surgical intervention (adjusted HR 0.65, $P = 0.003$), as well as overall death (adjusted HR 0.60, $P = 0.001$). These findings imply that post-pericardiocentesis colchicine therapy confers significant prognostic benefit ^[20].

Future research should further clarify the clinical role and therapeutic impact of colchicine among individuals presenting with pericardial effusion of diverse causes and stages, focusing on defining the most appropriate dose, initiation timing, and treatment duration, as well as its integration with adjunctive regimens to refine management strategies for pericardial effusion.

3.2. Coronary atherosclerotic heart disease

3.2.1. Stable coronary artery disease

Inflammation is a key component in the development of atherosclerosis. Among patients receiving statin therapy, vulnerable coronary plaques and inflammatory markers have been shown to predict major adverse cardiovascular events (MACE) more effectively than low-density lipoprotein cholesterol levels ^[21]. Therefore, the use of anti-inflammatory agents may contribute to improved cardiovascular outcomes.

The CANTOS trial ^[22] investigated the cardioprotective effects of canakinumab, a human monoclonal antibody targeting IL-1 β . Canakinumab effectively reduced levels of inflammatory biomarkers without significantly affecting lipid profiles or platelet function. Administered at a dose of 150 mg every three months, it significantly lowered the recurrence of cardiovascular events, providing the first evidence that targeting inflammatory pathways can reduce the risk of cardiovascular events.

Nidorf et al. (2013) conducted the LoDoCo study, which was the first to evaluate the use of low-dose colchicine in patients with stable coronary artery disease. A total of 532 patients were enrolled and treated with colchicine (0.5 mg twice daily). The study demonstrated that colchicine effectively prevented the occurrence of cardiac arrest and non-cardioembolic ischemic stroke, potentially through the inhibition of neutrophil function. These findings suggest that low-dose colchicine provides a preventive benefit against cardiovascular events in patients with stable coronary artery disease ^[23].

The LoDoCo2 trial further validated the efficacy of colchicine in patients with chronic coronary artery disease. This study enrolled 5,522 patients who were randomly assigned to receive either colchicine or a placebo. The results demonstrated that colchicine significantly reduced the risk of cardiovascular events, with effects consistent with those of previous anti-inflammatory therapies and other secondary prevention strategies. Notably, the benefits emerged early and continued to accumulate over time ^[24].

Currently, both U.S. and European guidelines recommend colchicine as an anti-inflammatory therapy for coronary artery disease ^[25, 26]; however, its clinical adoption remains lower compared with lipid-lowering therapy. In 2023, the U.S. FDA approved colchicine (Lodoco, 0.5 mg tablets) for the treatment of atherosclerotic cardiovascular disease, marking it as the first anti-inflammatory drug approved by the FDA for cardiovascular indications. The COLPCI trial ^[27], currently underway in China, aims to evaluate the efficacy and safety of different doses of colchicine in reducing cardiovascular events among patients undergoing PCI, and its results are highly anticipated.

3.2.2. Acute coronary syndrome

In acute coronary syndrome (ACS), the rupture or erosion of vulnerable plaques triggers intense local inflammation and neutrophil infiltration, accelerating plaque destabilization. Persistent inflammatory activity is a major determinant of post-myocardial infarction outcomes, and residual inflammatory burden has been strongly correlated with recurrent cardiovascular events ^[28,29]. Evidence suggests that a once-daily regimen of 0.5 mg colchicine may enhance plaque stabilization and dampen inflammatory signaling among individuals presenting with ACS. Kaivan et al. (2018) observed that colchicine improved coronary plaque morphology independently of intensive statin therapy ^[30]. In contrast, Jennife et al. (2020) reported modulation of specific microRNAs that could serve as novel therapeutic biomarkers ^[31].

Unlike earlier investigations that failed to demonstrate meaningful cardiovascular benefit ^[32], the COLCOT

trial found that colchicine therapy led to a significant reduction in cardiovascular event rates ^[33]. Furthermore, Yu et al. (2024), in the COLOCT trial, provided the first imaging-based evidence that colchicine increased fibrous cap thickness and diminished macrophage infiltration via anti-inflammatory mechanisms, thereby reinforcing non-culprit plaque stability and lowering the likelihood of recurrent adverse cardiac outcomes, particularly among patients with optimally managed LDL-C concentrations ^[34].

Taken together, current findings highlight colchicine's therapeutic promise in ACS; nevertheless, its clinical efficacy and optimal treatment parameters warrant further confirmation through large-scale trials.

3.3. Atrial fibrillation

Atrial fibrillation (AF) represents the most prevalent sustained cardiac arrhythmia, and its postoperative form frequently complicates the course of patients following cardiac surgery. The pathogenesis is believed to involve pericardial inflammation, autonomic dysregulation, and heightened catecholamine activity ^[17]. AF represents the most prevalent sustained cardiac arrhythmia, and its postoperative form frequently complicates the course of patients following cardiac surgery. The pathogenesis is believed to involve pericardial inflammation, autonomic dysregulation, and heightened catecholamine activity ^[35]. Wu et al. (2020) reported that colchicine shortened AF duration and reduced its occurrence through suppression of inflammatory cascades and attenuation of atrial fibrotic remodeling ^[10]. Moreover, a meta-analysis revealed that a low-dose colchicine regimen markedly decreased the incidence of postoperative AF among patients undergoing coronary artery bypass graft surgery ^[36]. Further research is warranted to clarify its prophylactic value and define the optimal timing and duration of administration.

3.4. Heart failure

Chronic heart failure represents the end stage of cardiovascular pathology and is characterized by progressive loss of cardiomyocytes and compromised myocardial contractility. Crosstalk between pro-inflammatory signaling, apoptotic pathways, and myocardial dysfunction drives disease progression, while targeting inflammation may help attenuate this process and improve long-term outcomes. Spyridon et al. (2014) reported that, although colchicine administration led to a marked reduction in circulating inflammatory mediators, including C-reactive protein (CRP) and interleukin-6 (IL-6) ^[37], no significant improvements were observed in functional capacity, survival, or hospital stay. Likewise, Pascual et al. (2024) observed that despite lowering systemic inflammatory activity, colchicine did not substantially influence the incidence of acute decompensation or worsening heart failure events ^[38].

3.5. Adverse cardiovascular events after revascularization

Revascularization procedures, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting, are often accompanied by postoperative complications such as restenosis, myocardial infarction, or arrhythmias, all of which continue to pose considerable clinical challenges. Endothelial trauma and subsequent inflammatory activation play central roles in these adverse outcomes, and accumulating evidence suggests that colchicine may alleviate such inflammatory sequelae. Shah and colleagues observed that administering colchicine prior to surgery attenuated postoperative increases in circulating inflammatory mediators—specifically IL-6 and CRP—although no substantial reduction in myocardial injury was detected ^[39]. Conversely, Giannopoulos and co-workers found evidence supporting a

modest protective effect of colchicine against postoperative myocardial damage ^[40]. In a comprehensive meta-analysis, Fu et al. (2021) concluded that colchicine therapy was associated with a lower rate of major adverse cardiovascular events (MACE) among patients undergoing PCI, while having no statistically significant influence on mortality, infarction recurrence, or restenosis ^[41]. Taken together, these findings indicate that colchicine shows promise as a prophylactic anti-inflammatory agent in mitigating post-revascularization cardiovascular complications, though its therapeutic efficacy requires confirmation in larger, rigorously designed clinical trials.

4. Safety and tolerability

Colchicine is an ancient drug that, despite its widespread use, may cause adverse events when overdosed due to its mitotic toxicity. In a large randomized controlled trial including 8,659 patients, 17.9% of those receiving colchicine experienced diarrhea, 1.9% had hepatic adverse events, and 4.2% developed myotoxicity, while no cases of neuropathy or death were reported ^[42]. In another trial involving 14,188 patients, the incidence of adverse events was slightly higher in the colchicine group (15.3% vs. 13.9%), with a significant increase in gastrointestinal events (16.1% vs. 12.2%), particularly diarrhea (12.5% vs. 8.1%); however, no significant differences were observed for other adverse outcomes ^[43]. A systematic review found no significant association between colchicine use and infectious adverse events ^[44], and long-term therapy did not increase the risk of sepsis or cancer ^[45]. Overall, colchicine has a favorable safety profile, but individualized dose adjustment, close monitoring of hepatic and renal function, and vigilance against overdose remain essential.

5. Summary and outlook

Colchicine, a long-established therapeutic agent with deep roots in traditional medicine, has undergone a remarkable resurgence in clinical relevance over the past decade. Originally utilized for disorders such as gout and familial Mediterranean fever, its medical scope has progressively expanded to include numerous systemic conditions, most notably cardiovascular pathologies. Currently, both its safety characteristics and diverse pharmacological actions are well substantiated, underscoring its growing importance in cardiovascular therapeutics. Owing to its accessibility, affordability, and convenient oral administration, colchicine possesses the potential to significantly influence global cardiovascular care, particularly within resource-limited regions. As ongoing research continues to elucidate its mechanisms and broaden clinical understanding, future advancements are likely to further extend the therapeutic landscape of colchicine in cardiovascular medicine.

Disclosure statement

The authors declare no conflict of interest.

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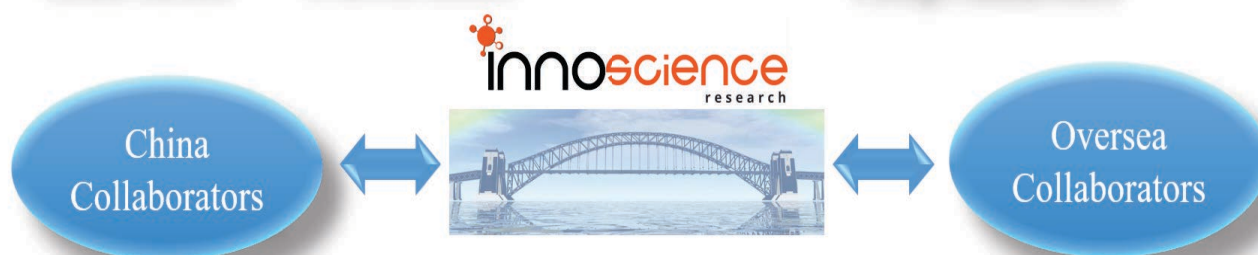
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