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ORIGINAL RESEARCH

# Association of Mitral Regurgitation with Postoperative Atrial Fibrillation in Critically Ill Noncardiac Surgery Patients: A Prospective Cohort Study

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**Purpose:** Atrial fibrillation (AF) is common in critically ill patients and can have serious consequences. Postoperative AF (POAF) in critically ill patients following noncardiac surgery has been understudied, contrary to cardiac procedures. Mitral regurgitation (MR) is associated with left ventricular dysfunction, which might contribute to the occurrence of AF in postoperative critically ill patients. This study aimed to investigate the association between MR and POAF in critically ill noncardiac surgery patients and establish a new nomogram for the prediction of POAF in critically ill noncardiac surgery patients.

**Patients and Methods:** A prospective cohort of 2474 patients who underwent thoracic and general surgery was enrolled in this study. Data on preoperative transthoracic echocardiography (TTE), electrocardiogram (ECG), and several commonly utilized scoring systems (CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST) and baseline clinical data were collected. Independent predictors were selected by univariate and multivariable logistic regression analysis, and a nomogram was constructed for POAF within 7 days after postoperative intensive care unit (ICU) admission. The ability of the MR-nomogram and other scoring systems to predict POAF was compared by receiver operator characteristic (ROC) curve analysis and decision curve analysis (DCA). Additional contributions were evaluated by integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analysis.

**Results:** A total of 213 (8.6%) patients developed POAF within 7 days after ICU admission. Compared to CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST scoring systems, MR-nomogram showed better predictive ability for POAF with an area under the ROC curve of 0.824 (95% confidence interval: 0.805–0.842, $p < 0.001$). The improvement of the MR-nomogram in predictive value was supported by NRI and IDI analysis. The net benefit of the MR nomogram was maximal in DCA.

**Conclusion:** MR is an independent risk factor of POAF in critically ill noncardiac surgery patients. The nomogram predicted POAF better than other scoring systems.

**Keywords:** postoperative atrial fibrillation, mitral regurgitation, critically ill patients, predictive nomogram

## Introduction

Atrial fibrillation (AF) is the most common complication in intensive care units (ICUs).[1,2] Observational studies have suggested that the occurrence of AF is 5–26% in noncardiac ICUs[3,4] and up to 10% in surgical ICUs.[5] The mechanisms that promote the development of postoperative AF (POAF) in critically ill patients are complex and multi-factorial. Many potential mechanisms have been implicated, including atrial ischemia, increased catecholamines, inflammation, and increased atrial pressure.[6,7] According to recent studies, patients with left atrial (LA) or left ventricular (LV) dysfunction were vulnerable to AF under the impact of surgery or inflammation.[8–10] Experimental and clinical observations have

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demonstrated that increased atrial stretch induced by increased atrial pressure shortens the atrial refractory period and may play an important role in AF development.[11] Mitral regurgitation (MR) has been reported as a marker of increased LA filling pressure.[12] On the other hand, LV diseases cause global dilatation or regional remodeling of the LV, which can also result in secondary MR.[13,14] In the canine model of MR, the LA size increases with a corresponding decrease in LV systolic function, and elevated atrial activation lowers the effective refractory period and increases the inducibility of AF.[5,15] These findings demonstrate that the influence of MR on AF cannot be ignored. Based on previous studies, we speculate that MR is a risk factor for POAF and has great prediction value. Recent studies have shown that MR was associated with AF recurrence after ablation.[16,17] Bahouth et al have also found that there was a graded independent association between MR severity and new-onset AF in patients with acute myocardial infarction.[12] Similarly, after analysis of acute decompensated heart failure hospitalization, the prevalence of AF increased with increased MR severity.[18] Although previous studies have clarified the relationship between MR and AF, few studies have been performed in postoperative critically ill patients. Additionally, no prior study has established the prediction model using MR in POAF patients.

At present, it has been reported that advanced age, sex, previous cardiac arrhythmias, pre-existing cardiorespiratory disease, myocardial ischemia, and perioperative factors, as well as MR, are significant risk factors for developing new-onset POAF in patients.[19] Currently, there has been a non-validated model to predict POAF in critically ill patients. Recent studies have created and validated several models to predict POAF after cardiac surgery, such as HATCH[20] and COM-AF.[21] HART has been used to predict POAF after noncardiac elective surgery.[22] C2HEST has been detected with the potential to be utilized as a risk stratification tool for decision-making regarding a screening approach for AF in stroke.[23] Moreover, the CHA2DS2-VASc score, initially created to predict the risk of thromboembolism in patients with AF, has been validated for the prediction of AF.[24] However, there is no appropriate model to predict critically ill patients after noncardiac surgery. We hypothesized that MR plays a vital role in POAF prediction in thoracic and general surgery postoperative critically ill patients.

To test this hypothesis, in this study, we demonstrated that MR is an independent risk factor and a strong predictor of POAF. Multiple scoring systems have been proposed to predict POAF occurrence, with modest predicting power. We further created an MR-centered nomogram to predict POAF and demonstrated the superiority of this nomogram to the existing scoring system in a prospective cohort of thoracic and general surgery postoperative critically ill patients.

## Materials and Methods

The present study was approved by the Human Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (Beijing, China) (approval no. 2020-ke-236), and written informed consent was obtained from each individual or their representative before enrolling in the study.

### Study Design and Patients' Population

The study was designed, performed, and reported following the STROBE reporting guidelines and in accordance with the Helsinki Declaration.[25] It was performed in a 20-bed surgical ICU at Beijing Chaoyang Hospital from January 1, 2018, to December 31, 2021. We continuously screened postoperative adult patients who underwent general and thoracic surgery. Patients had multiple ICU admissions or were included only once. The exclusion criteria were age < 18 years; AF or flutter detected in preoperative examination or electrical monitoring during surgery; received amiodarone before operation; the presence of a cardiac implantable electronic device with a functioning atrial lead (pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device); underwent transplantation surgery; or none critical data (missing data of electrocardiogram [ECG], ultrasonic cardiogram, and baseline data before admission).

### Definitions and Clinical Endpoints

POAF was defined as any AF episode lasting > 30 seconds on 12-lead surface ECG or telemetry monitoring or when the patient referred symptoms during a hospital stay.[26] All patients had continuous bedside electronic monitoring at least during the first 24 hours after ICU admission. All arrhythmic events were adjusted by cardiologists.

The primary endpoint was the development of POAF from the time of arrival in the ICU admission to postoperative day 7. The secondary endpoints included postoperative complications such as infection, fistula,

postoperative bleeding, myocardial infarction, acute kidney injury (AKI), duration of mechanical ventilation and ICU and hospital stays, and hospital mortality.

## Data Collection

Previous studies have suggested that demographic information,[27] clinical data, medications,[28] and complications[29] were associated with the incidence of POAF. Preoperative cardiac function was assessed by ECG (including sinus tachycardia, sinus bradycardia, arrhythmia, myocardial ischemia, conduction block, P-wave, PR interval, and QTc interval) and ultrasonic cardiogram (UCG) (including MR, tricuspid regurgitation [TR], LV mass, segmental wall motion abnormality, left atrium [LA] volume, LV ejection fraction [LVEF], rheumatic heart disease, pulmonary hypertension, aortic sinus inner diameter, and E/A]). Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were used to estimate the severity of the patient's illness on the day of ICU admission. Clinical variables containing prior health history, thoracic surgery, surgery procedure, laboratory blood tests, postoperative complications, duration of mechanical ventilation, ICU stay, and hospital stays were collected from the electronic medical record system.

Echocardiography was performed by an experienced sonographer who had received advanced training and certification in echocardiographic imaging, according to the guidelines of the American Society of Echocardiography (ASE). M-mode echocardiography was used to measure LA dimensions, and the LVEF was calculated with Simpson's method. Doppler echocardiography assessed early (E) and late (A) diastolic mitral inflow velocities and the E/A ratio.[30,31]

## Risk Scoring System

The scores were calculated as follows. The CHA2DS2-VASc score comprised a history of coronary heart failure (CHF): 1 point; hypertension (HT): 1 point, diabetes: 1 point; age 65–74 years: 1 point, age ≥ 75 years: 2 points; female sex: 1 point; peripheral vascular disease: 1 point; stroke/transient ischemic attack (TIA): 2 points.[24,32] The C2HEST score comprised coronary artery disease (CAD): 1 point; chronic obstructive pulmonary disease (COPD): 1 point; HT: 1 point; age ≥ 75 years: 2 points; systolic HF: 2 points; thyroid disease: 1 point.[33] The COM-AF score comprised age 65–74 years: 1 point, aged ≥ 75 years: 2 points; CHF: 2 points; female sex: 1 point; HT: 1 point; diabetes: 1 point; previous stroke: 2 points.[21] The HATCH score comprised stroke or TIA: 2 points; HT 1 point; CHF: 2 points; age ≥ 75 years: 1 point; COPD: 1 point.[34] The HART score comprised HT 1 point; age 65–74 years: 1 point, age ≥ 75 years: 2 points; intermediate risk surgery: 3 points, high-risk surgery: 3 points; thyroid dysfunction: 1 point.[22]

## Covariates Identified by Directed Acyclic Graphs (DAGs)

Recently, it has been reported that directed acyclic graphs (DAGs) can identify confounding variables and mediators in exposure-outcome relationships, reduce confounding bias, and avoid over-adjustment.[35–37] By reviewing possible causal mechanisms reported by previously published studies, we constructed a DAG framework to evaluate the effects of MR on the occurrence of POAF. After selecting the variables, directed paths were created according to standard procedures and analyzed with DAGitty 3.0 software (http://www.dagitty.net) (Figure 1).

## Statistical Analysis

SPSS v25 (SPSS Inc, Chicago, IL, USA), MedCalc v.16.4.3 (MedCalc, Ostend, Belgium), and R 4.0.3 (R Project for Statistical Computing, Vienna, Austria) were used for statistical analysis. Categorical variables were presented as percentiles, and continuous variables were presented as a median with the 25th and 75th percentiles (interquartile range [IQR]). Mann–Whitney *U*-test was used to compare continuous data between groups, and the chi-squared test or Fisher's exact test was used to compare categorical data. Univariate logistic regression was used to assess the correlation between variables and POAF. Due to DAGs, we selected minimal sufficient adjustment sets to evaluate the effects of MR on POAF. Excluding the mediator variables of MR and POAF, clinical parameters with $p < 0.05$ in the univariate analysis were added to the multivariate logistic regression model. A nomogram evaluating POAF was established based on the multivariate analysis using the rms package in R. The predictive accuracy of the nomogram was assessed by calibration. Receiver operator characteristic (ROC) curve analysis was used to assess the predictive value of the MR-nomogram and

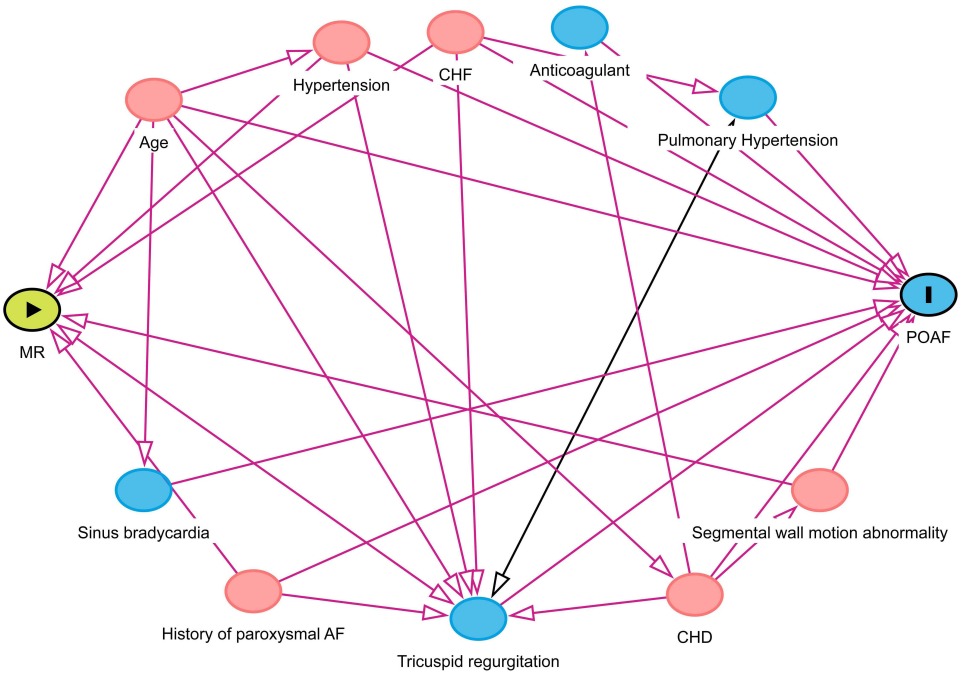


**Figure 1** Directed acyclic graph of mitral regurgitation and postoperative atrial fibrillation.
**Abbreviations**: MR, mitral regurgitation; CHF, congestive heart failure; POAF, postoperative atrial fibrillation; CHD, coronary heart disease.

other scoring systems for POAF. The net contribution of the nomogram was assessed using the Hosmer-Lemeshow test. Bootstrapping with repeated sampling was performed to confirm the stability of the nomogram. The area under the ROC curve (AUC), sensitivity, specificity, and their corresponding 95% confidence intervals (CIs),[38] defined as follows: 0.90–1.0, excellent; 0.80–0.89, good; 0.70–0.79, useful; 0.60–0.69, poor; and 0.50–0.59, not useful, were determined.[39] The cutoff point was the value with the highest specificity and sensitivity. Improvement in the predictive accuracy of the nomogram was evaluated by calculating the relative integrated discrimination improvement (IDI) and net reclassification improvement (NRI).[40] We also estimated the clinical utility and net benefit of the new prediction nomogram by decision curve analysis (DCA), which identifies patients at risk of POAF based on the new prediction nomogram and other scoring systems. For all analyses, statistical significance was taken as a two-sided p-value $< 0.05$.

# Results

## Overall Patient Characteristics

A total of 6885 subjects who were admitted to the ICU postoperatively were screened. Among them, 3268 adult patients underwent general or thoracic surgery. A total of 794 patients were excluded for the following reasons: AF or atrial flutter in admission ECG (n = 37); receiving amiodarone prior to surgery (n = 45); the presence of a cardiac implantable electronic device with a functioning atrial lead (pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device) (n = 23); undergoing transplantation surgery (n = 593); noncritical data before surgery (n = 96). Thus, 2474 patients were ultimately enrolled in the prospective cohort. Their baseline characteristics are shown in Table 1. The flow diagram is shown in Figure 2.

In total, 213 patients (8.6%) met the primary endpoint of POAF. There was a statistically significant difference in the postoperative comorbidities, including infection (27.2% vs 10.0%, $p < 0.001$), fistula (15.0% vs 6.8%, $p < 0.001$), postoperative bleeding (7.5% vs 3.1%, $p = 0.001$), myocardial infarction (6.6% vs 1.9%, $p < 0.001$), and AKI (8.5% vs 1.2%, $p < 0.001$). The duration of mechanical ventilation (15.4 [6.2–24.1] vs 9.42 [3.32–16.18], $p < 0.001$), ICU stay (94.9 [46.9–165.5] vs 46.2 [24.0–83.2], $p < 0.001$), and hospital stay (554.0 [405.0–865.0] vs 463.0 [342.0–673.0], $p < 0.001$) was longer in patients with POAF than that in patients without POAF (Table 2).

**Table 1** Baseline Characteristics of Patients Stratified by Postoperative Atrial Fibrillation

| Variables | All n=2474 | POAF n=213 | Non POAF n=2261 | *P* value |
|---|---|---|---|---|
| Age, years, median (IQR) | 67 (59–74) | 73 (67–80) | 66 (58–73) | <0.001[b] |
| Male, n (%) | 1537 (62.1) | 133 (62.4) | 1404 (62.1) | 0.921[a] |
| BMI, kg/m2, median (IQR) | 23.5 (21.2–26.0) | 23.7 (21.5–26.0) | 23.5 (21.2–26.0) | 0.516[b] |
| Chronic comorbidities | | | | |
| Hypertension, n (%) | 1197 (48.4) | 130 (61.0) | 1067 (47.2) | <0.001[a] |
| Diabetes, n (%) | 560 (22.6) | 55 (25.8) | 505 (22.3) | 0.245[a] |
| Coronary heart disease, n (%) | 280 (11.3) | 37 (17.4) | 243 (10.7) | 0.004[a] |
| COPD/asthma, n (%) | 109 (4.4) | 11 (5.2) | 98 (4.3) | 0.573[a] |
| Congestive heart failure, n (%) | 314 (12.7) | 78 (36.7) | 236 (10.4) | <0.001[a] |
| Stroke/TIA, n (%) | 223 (9.0) | 24 (11.) | 199 (8.8) | 0.230[a] |
| Hyperlipidemia, n (%) | 62 (2.5) | 6 (2.8) | 56 (2.5) | 0.761[a] |
| History of paroxysmal atrial fibrillation, n (%) | 35 (1.4) | 17 (8.0) | 18 (0.8) | <0.001[a] |
| Chronic kidney disease, n (%) | 41 (1.7) | 2 (0.9) | 39 (1.7) | 0.390[a] |
| Thyroid disease, n (%) | 18 (0.7) | 2 (0.9) | 16 (0.7) | 0.467[a] |
| Thoracic surgery, n (%) | 298 (12.0) | 55 (25.8) | 243 (10.7) | <0.001[a] |
| Smoking, n (%) | 481 (19.4) | 29 (13.6) | 452 (20.0) | 0.025[a] |
| Alcohol, n (%) | 420 (17.0) | 45 (21.1) | 375 (16.6) | 0.091[a] |
| Medication before surgery | | | | |
| Anticoagulant, n (%) | 160 (6.5) | 24 (11.3) | 136 (6.0) | 0.003[a] |
| Statin, n (%) | 151 (6.1) | 21 (9.9) | 130 (10.2) | 0.017[a] |
| β blocker, n (%) | 97 (3.9) | 13 (6.1) | 84 (3.7) | 0.086[a] |
| Preoperative ECG | | | | |
| Sinus tachycardia, n (%) | 66 (2.7) | 3 (1.4) | 63 (2.8) | 0.233[a] |
| Sinus bradycardia, n (%) | 146 (5.9) | 3 (1.4) | 143 (6.3) | 0.004[a] |
| Arrhythmia, n (%) | 217 (8.8) | 27 (12.7) | 190 (8.4) | 0.035[a] |
| Myocardial ischemia, n (%) | 495 (20.0) | 45 (21.1) | 450 (19.9) | 0.669[a] |
| Conduction block, n (%) | 116 (4.7) | 8 (3.8) | 108 (4.8) | 0.500[a] |
| P-wave, m·s, median (IQR) | 92 (86–100) | 96 (87–100) | 92 (86–100) | 0.139[b] |
| PR interval, s, median (IQR) | 156.0 (142.0–174.0) | 164.0 (146.0–181.5) | 156.0 (142.0–174.0) | 0.034[b] |
| QTc interval, m·s, median (IQR) | 416.0 (398.0–432.0) | 423.5 (405.5–434.8) | 415.0 (398.0–432.0) | 0.016[b] |
| Echocardiographic parameters | | | | |
| Mitral regurgitation, n (%) | 381 (15.4) | 56 (26.3) | 325 (14.4) | <0.001[a] |
| Tricuspid regurgitation, n (%) | 735 (29.7) | 100 (46.9) | 635 (28.1) | <0.001[a] |
| LV mass, grams, median (IQR) | 144.5 (122.3–170.2) | 147.8 (125.0–169.9) | 143.9 (122.2–170.2) | 0.960[b] |
| Segmental wall motion abnormality, n (%) | 76 (3.1) | 13 (6.1) | 63 (2.8) | 0.007[a] |
| LA volume, mL, median (IQR) | 30.3 (25.2–37.2) | 31.8 (25.0–41.4) | 30.2 (25.2–37.0) | 0.120[b] |
| LV ejection fraction (%) | 68.0 (64.0–71.0) | 66.0 (63.0–70.0) | 68.0 (64.0–71.0) | 0.128[b] |
| Rheumatic heart disease, n (%) | 6 (0.2) | 2 (0.9) | 4 (0.2) | 0.088[a] |
| Pulmonary hypertension, n (%) | 108 (4.4) | 29 (13.6) | 79 (3.5) | <0.001[a] |
| Aortic sinus inner diamete, r mm, median (IQR) | 32.0 (30.0–34.0) | 32.0 (31.0–35.0) | 32.0 (30.0–34.0) | 0.128[b] |
| E/A ratio, median (IQR) | 0.76 (0.65–0.93) | 0.72 (0.56–0.94) | 0.76 (0.65–0.93) | 0.030[b] |
| Preoperative biochemical data | | | | |
| CTNI, ng/mL, median (IQR) | 0.0 (0.0, 0.01) | 0.0 (0.0, 0.03) | 0.0 (0.0, 0.01) | 0.599[b] |
| BNP, pg/mL, median (IQR) | 53.0 (26.0, 108.0) | 58.0 (38.0, 316.5) | 53.0 (25.8, 105.0) | 0.236[b] |
| Serum K+, mmol/L, median (IQR) | 4.0 (3.7, 4.4) | 4.1 (3.8, 4.5) | 4.0 (3.7, 4.3) | 0.214[b] |

(*Continued*)

**Table 1** (Continued).

| Variables | All n=2474 | POAF n=213 | Non POAF n=2261 | *P* value |
|---|---|---|---|---|
| Surgical data | | | | |
| Surgery time, hours median (IQR) | 3.5 (2.4–5.5) | 3.7 (2.4–5.8) | 3.5 (2.4–5.5) | 0.734[b] |
| Catecholamine, n (%) | 1301 (52.6) | 118 (55.4) | 1183 (52.3) | 0.390a |
| Etomidate, mg, median (IQR) | 0.0 (0.0–12.0) | 0.0 (0.0–10.0) | 0.0 (0.0–12.0) | 0.543[b] |
| Hormone, n (%) | 712 (28.8) | 71 (33.3) | 641 (28.4) | 0.125[a] |
| Esmolol, n (%) | 319 (12.9) | 19 (8.9) | 300 (13.3) | 0.070[a] |
| Cedilanid, n (%) | 57 (2.3) | 16 (7.5) | 41 (1.8) | <0.001[a] |
| Blood loss, mL, median (IQR) | 100.0 (50.0–300.0) | 200.0 (50.0–400.0) | 100.0 (50.0–300.0) | 0.012[b] |
| Urine volume, mL, median (IQR) | 500.0 (255.0–800.0) | 500.0 (300.0–850.0) | 450.0 (250.0–800.0) | 0.263[b] |
| Red cell infusion volume, mL, median (IQR) | 0.0 (0.0–200.0) | 0.0 (0.0–400.0) | 0.0 (0.0–0.0) | 0.003[b] |
| Plasma infusion volume, mL median (IQR) | 0.0 (0.0–0.0) | 0.0 (0.0–400.0) | 0.0 (0.0–0.0) | 0.010[b] |
| Liquid balance, mL, median (IQR) | 1815.0 (1350.0–2600.0) | 1980.0 (1450.0–2850.0) | 1815.0 (1350.0–2550.0) | 0.014[b] |
| Serum K+, mmol/L, median (IQR) | 3.8 (3.5–4.1) | 3.8 (3.6–4.1) | 3.8 (3.5–4.0) | 0.201[b] |
| Serum Ca+, mmol/L, median (IQR) | 1.1 (1.1–1.17) | 1.1 (1.1–1.2) | 1.1 (1.1–1.2) | 0.670[b] |
| Admission characteristics | | | | |
| APACHE II score, median (IQR) | 11.0 (9.0–14.0) | 12.0 (10.0–16.0) | 11.0 (9.0–14.0) | <0.001[b] |
| SOFA score, median (IQR) | 2.0 (0.0–3.0) | 2.0 (1.0–4.0) | 2.0 (0.0–3.0) | <0.001[b] |
| Heart rate, bpm, median (IQR) | 76.0 (66.0–89.0) | 80.0 (65.0–95.0) | 76.0 (66.0–89.0) | 0.044[b] |
| MAP, mmHg, median (IQR) | 100.0 (90.0–112.0) | 96.0 (85.0–106.5) | 101.0 (91.0–113.0) | <0.001[b] |
| CTNI, ng/mL, median (IQR) | 0.0 (0.0–0.01) | 0.01 (0.0–0.04) | 0.0 (0.0–0.01) | <0.001[b] |
| BNP, pg/mL, median (IQR) | 61.0 (32.0–121.0) | 99.0 (49.5–246.8) | 58.0 (31.0–114.0) | <0.001[b] |
| Oxygenation index, median (IQR) | 371.1 (262.1–472.0) | 330.0 (227.5–469.5) | 372.5 (265.0–472.0) | 0.023[b] |

**Notes**: [a]Chi-square test. [b]Mann–Whitney *U*-test.

**Abbreviations**: IQR, interquartile range; n, number of patients; BMI, body mass index; POAF, postoperative atrial fibrillation; TIA, transient ischemic attack; ECG, electrocardiogram; LV, left ventricular; LA, left atrium; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; MAP, mean arterial pressure.

## Identification of MR as a Predictive Factor for POAF

We identified MR on UCG related to POAF by using univariable analysis. Additionally, the presence of POAF was also associated with age, hypertension, coronary heart disease, CHF, history of paroxysmal AF, anticoagulant use, sinus bradycardia on ECG, TR on UCG, segmental wall motion abnormality on UCG, pulmonary hypertension on UCG, thoracic surgery, blood loss during surgery, red cell infusion volume during surgery, plasma infusion volume during surgery, liquid balance during surgery, cedilanid during surgery, APACHE II score at ICU admission, SOFA score at ICU admission, heart rate at ICU admission, mean arterial pressure (MAP) at ICU admission, and BNP at ICU admission (see Table S1). The DAG showed confounding factors for MR in POAF, including age, HT, CHF, history of paroxysmal AF, CHD, and segmental wall motion abnormality (Figure 1). Thus, of these variables, MR on UCG, age, history of paroxysmal AF, CHF, thoracic surgery, blood loss, heart rate at ICU admission, and MAP at ICU admission were independent predictors of POAF, which were identified by multivariable analysis (see Table S2). Hosmer-Lemeshow goodness-of-fit test ($p > 0.05$) was used to confirm the calibration of the MR nomogram. This MR-nomogram predicted POAF with an AUC of 0.824 (95% CI: 0.805–0.842, $p < 0.001$).

The predictive nomogram combining all significant independent predictive factors for POAF is shown in Figure 3. A sum score could be calculated as the total scores of related predictors and referred to the probability of POAF in the basal axis. For example, in an 80-year-old MR patient without a history of paroxysmal AF or CHF undergoing thoracic surgery with intraoperative 5000-mL blood loss on admission to ICU with an HR of 100 bpm and MAP of 60 mm Hg, the total score would be 210 and POAF probability was approximately 85%. The calibration plot for the probability of POAF showed optimal agreement between the prediction by the MR-nomogram and actual observation. Remarkably, the

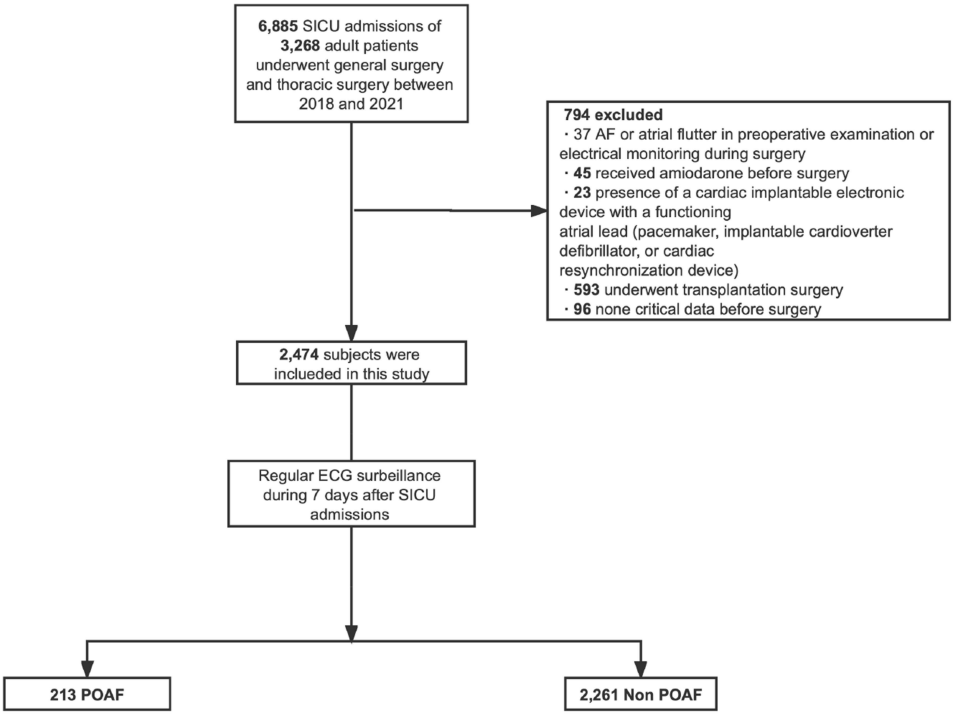


**Figure 2** Patient selection flow.
**Abbreviations**: SICU, surgical intensive care unit; AF, atrial fibrillation; ECG, electrocardiogram; POAF, postoperative atrial fibrillation.

calibration plot for the probability of POAF showed good consistency between the MR-nomogram prediction and actual observation (Figure 4).

## Predictive Performance of the MR Nomogram Compared to Other Scoring Systems

The scores of CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST were significantly higher in patients with POAF compared with patients without POAF (Table 3). The AUCs for the MR nomogram and other scoring systems are shown in Figure 5. The MR nomogram had an AUC of 0.824 (95% CI: 0.805–0.842, P < 0.001) for predicting POAF. In

**Table 2** Outcomes Between Patients with and without Postoperative Atrial Fibrillation

| Variables | All n=2474 | POAF n=213 | Non POAF n=2261 | *P* value |
|---|---|---|---|---|
| Infection, n (%) | 283 (11.4) | 58 (27.2) | 225 (10.0) | <0.001[a] |
| Fistula, n (%) | 185 (7.5) | 32 (15.0) | 153 (6.8) | <0.001[a] |
| Postoperative Bleeding, n (%) | 86 (3.5) | 16 (7.5) | 70 (3.1) | 0.001[a] |
| Myocardial infarction, n (%) | 58 (2.3) | 14 (6.6) | 44 (1.9) | <0.001[a] |
| Acute kidney injury, n (%) | 46 (1.9) | 18 (8.5) | 28 (1.2) | <0.001[a] |
| Length of ICU, hours, median (IQR) | 47.2 (24.3–89.6) | 94.9 (46.9–165.5) | 46.2 (24.0–83.2) | <0.001[b] |
| Length of hospital, hours, median (IQR) | 481.0 (342.1–678.0) | 554.0 (405.0–865.0) | 463.0 (342.0–673.0) | <0.001[b] |
| Hospital mortality, n (%) | 26 (1.1) | 4 (1.9) | 22 (1.0) | 0.216[a] |
| Mechanical ventilation, hours, median (IQR) | 10.0 (3.4–16.7) | 15.4 (6.2–24.1) | 9.42 (3.32–16.18) | <0.001[b] |

**Notes**: [a]Chi-square test. [b]Mann–Whitney *U*-test.
**Abbreviations**: IQR, interquartile range; n, number of patients; POAF, postoperative atrial fibrillation; ICU, intensive care unit.

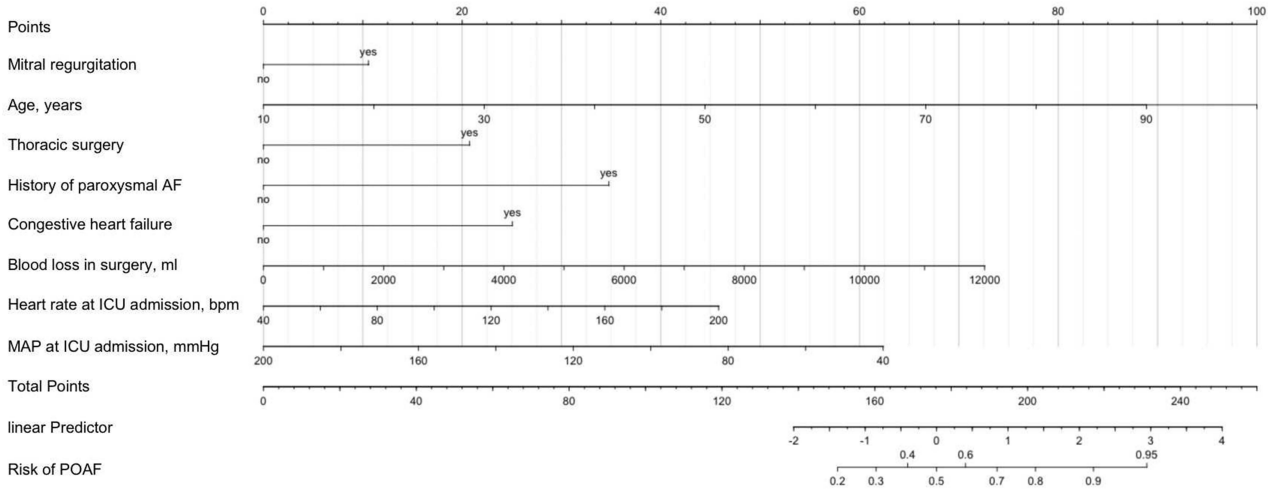


**Figure 3** Nomogram for POAF risk and its predictive performance. Each variable is assigned a point on the top axis by drawing a line upward. The sum of these numbers is located on the Total Points axis, and a line is drawn downwards to the Probability axis to identify the likelihood of POAF in postoperative critically ill patients.
**Abbreviations**: POAF, postoperative atrial fibrillation, ICU intensive care unit, MAP, mean arterial pressure; AF, atrial fibrillation.

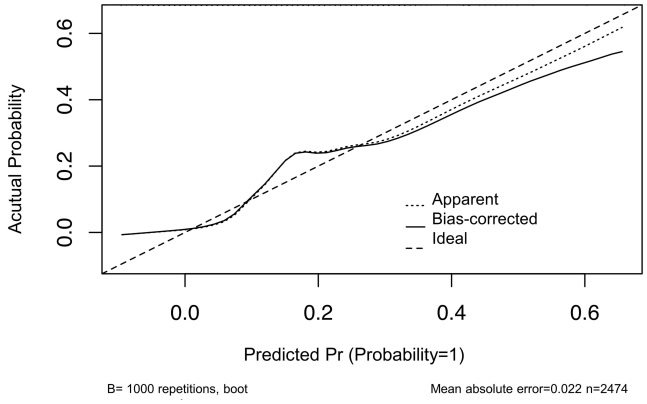


**Figure 4** MR-nomogram calibration curves for predicting postoperative atrial fibrillation among critically ill patients. MR-Nomograms-predicted probability of POAF is plotted on the x-axis, and actual probability is plotted on the y-axis.
**Abbreviation**: MR, mitral regurgitation.

contrast, CHA2DS-VASc, HATCH, COM-AF, C2HEST, and HART showed lower performance in predicting POAF, with AUCs of 0.668 (95% CI: 0.646–0.691, P < 0.001), 0.671 (95% CI: 0.648–0.693, P < 0.001), 0.687 (95% CI: 0.664–0.708, P < 0.001), 0.702 (95% CI: 0.680–0.724, P < 0.001), and 0.669 (95% CI: 0.646–0.691, P < 0.001), respectively.

**Table 3** Other Scoring Systems in POAF and Non POAF Patients

| | All n=2474 | POAF n=213 | Non POAF n=2261 | *P* value |
|---|---|---|---|---|
| C2HEST, median (IQR) | 1 (0–2) | 2 (1–3) | 1 (0–2) | <0.001[a] |
| CHA2DS-VASc, median (IQR) | 2 (1–3) | 3 (2–4) | 2 (1–3) | <0.001[a] |
| COM-AF, median (IQR) | 2 (1–3) | 3 (2–5) | 2 (1–3) | <0.001[a] |
| HART, median (IQR) | 4 (3–4) | 4 (4, 5) | 4 (3–4) | <0.001[a] |
| HATCH, median (IQR) | 1 (0–2) | 2 (1–2.75) | 1 (0–2) | <0.001[a] |

**Note**: [a]Mann–Whitney *U*-test.
**Abbreviations**: IQR, interquartile range; n, number of patients; POAF, postoperative fibrillation.

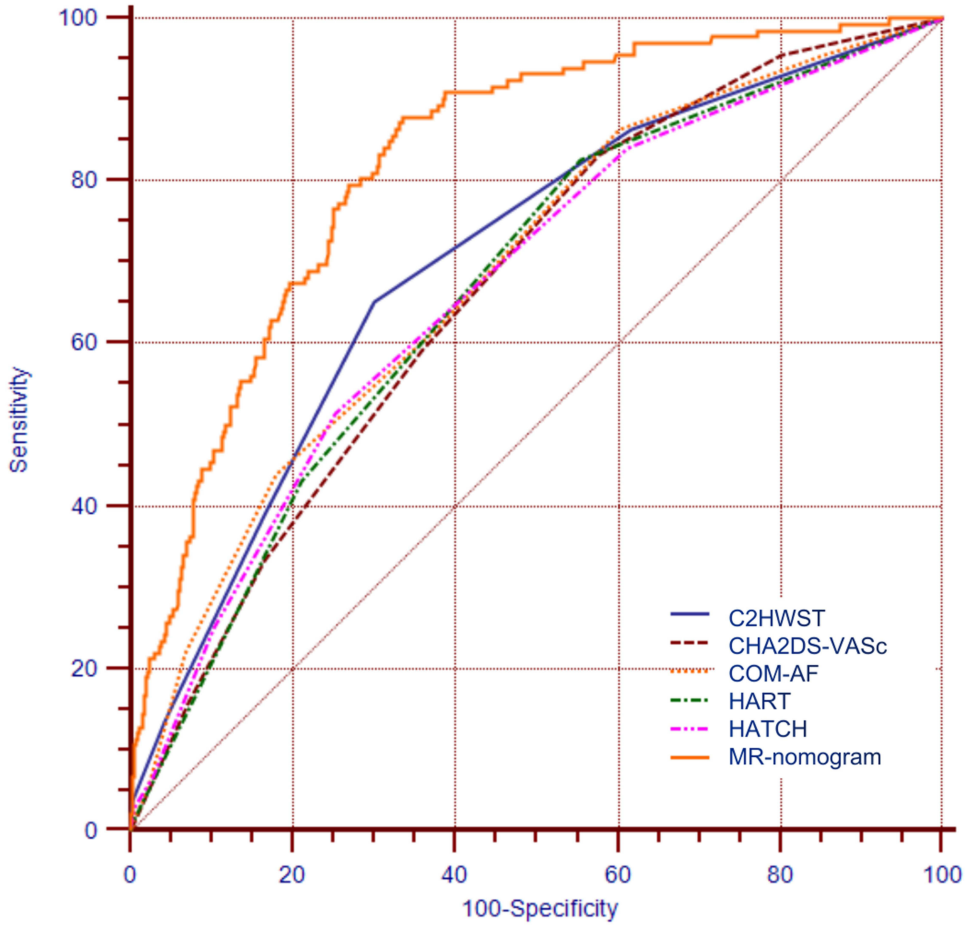


**Figure 5** Predictive value of MR-nomogram and other score system for POAF.
**Abbreviations**: ROC, receiver operator characteristic; AUC, area under the ROC curve.

The statistical significance of the difference between AUCs of the MR-nomogram and other scoring systems was supported by the DeLong method, IDI, and NRI ($P < 0.001$ for each scoring system and new nomogram) (Table 4).

## Predictive Superiority of the MR Nomogram Over Other Scoring Systems

We conducted DCA to further investigate the clinical utility of the MR nomogram and other scoring systems in predicting POAF. DCA revealed that the new MR nomogram had the highest net benefit at 10–50% of the probability threshold (Figure 6); that is, if a patient with a risk of POAF between 10% and 50% warranted further therapy (such as

**Table 4** Comparison of the ROC Curves, NRI and IDI of Model vs Other Score Systems in Predicting POAF

| | DeLong | NRI | *P* for NRI | IDI | *P* for IDI |
|---|---|---|---|---|---|
| MR-nomogram vs CHA2DS-VASc | <0.001 | 0.1565 (0.0881–0.2249) | <0.001 | 0.0844 (0.0491–0.1196) | <0.001 |
| MR-nomogram vs HATCH | <0.001 | 0.1351 (0.07–0.2001) | <0.001 | 0.0791 (0.0459–0.1123) | <0.001 |
| MR-nomogram vs COM-AF | <0.001 | 0.1502 (0.0828–0.2176) | <0.001 | 0.0744 (0.0407–0.1082) | <0.001 |
| MR-nomogram vs C2HEST | <0.001 | 0.1338 (0.0687–0.1988) | <0.001 | 0.0634 (0.03–0.0968) | <0.001 |
| MR-nomogram vs HART | <0.001 | 0.1622 (0.096–0.2284) | <0.001 | 0.08 (0.0443–0.1157) | <0.001 |

**Abbreviations**: MR, mitral regurgitation; ROC, receiver operator characteristic; POAF, postoperative atrial fibrillation; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

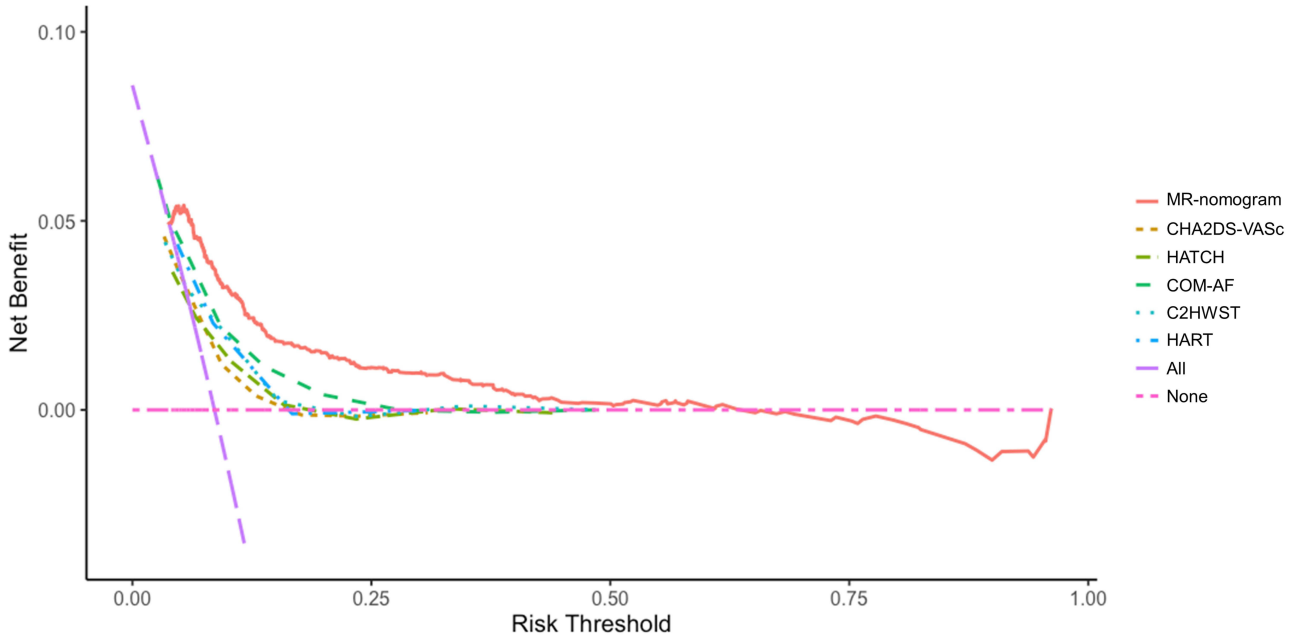


**Figure 6** Decision curve for prediction of POAF using different prediction models. The x axis shows threshold values for POAF while the y axis represents the net benefit for the different threshold values of POAF; a higher net benefit is provided by new prediction nomograms that are farthest away from the slanted dashed gray line (assuming all adverse events) and horizontal black line (assuming no adverse event).
**Abbreviation**: MR, mitral regurgitation.

preventive interventions or hemodynamic monitoring), POAF screening using the MR nomogram showed a better benefit with a wide range of threshold probabilities and better performances than CHA2DS-VASc, HATCH, COM-AF, C2HEST, and HART. Although the net benefits of the six models increased similarly with increasing probability thresholds, they deviated significantly at low probability thresholds.

## Sensitivity Analysis

As the history of paroxysmal AF may affect MR, we concluded that MR was an independent risk factor (odds ratio [OR] = 1.750, 95% CI: 1.085–2.821, p = 0.022) after excluding MR patients with a history of paroxysmal AF (n = 12) and repeating the risk prediction analysis. Moreover, the MR nomogram also showed a useful value for predicting POAF (AUC = 0.823 [0.790–0.857], p < 0.001).

# Discussion

AF is the most common sustained dysrhythmia independently associated with poor prognosis in critically ill patients. A total of 8.6% of critically ill adult patients experienced AF within 7 days after surgery in our study, similar to a previous report.[7] AF is the risk factor for in-hospital mortality and long-term mortality in elderly patients undergoing hip fracture surgery.[41,42] In our study, although POAF did not show an influence on mortality, it was associated with perioperative myocardial infarction, acute kidney injury, and complications, such as infection, fistula, and bleeding. Patients with AF had prolonged mechanical ventilation time, ICU, and hospital length of stay. New-onset POAF can be a marker of increased illness severity.[43,44] However, early identification of high-risk patients can lead to initiating preventive measures (eg, utilizing drugs such as beta-blockers, statins, oral anticoagulants, antiarrhythmics, and electrolyte supplementation[45]) before adverse cardiac events to reduce mortality and improve clinical outcomes. Prophylactic amiodarone used in high-risk individuals effectively reduced the incidence of POAF, improved outcomes, and reduced the associated health resource utilization and costs.[46] We first constructed an accurate nomogram combining MR based on DAGs and multivariate logistic regression to predict POAF following thoracic and general surgery in critically ill patients.

MR involves the retrograde blood flow from the LV into the LA,[47] leading to volume overload in the LV and LA, which may serve as a predictor of LA enlargement and remodeling.[48,49] LA remodeling predicts adverse cardiovascular outcomes and thus can be utilized as a marker to monitor diseased states.[50] LA enlargement, remodeling, and dysfunction promote a milieu conducive to AF.[51] A previous study has shown that patients with MR had a substantial risk (up to 28%) of AF post-ablation recurrence.[49] Patients with MR have a spherical atrium, which is associated with a higher rate of AF.[52] In our large cohort of postoperative critically ill patients, we demonstrated MR as an independent risk factor for POAF. This was the first study to investigate the association between MR and POAF in postoperative critically ill patients.

Besides, we also identified the following independent risk factors associated with POAF: age, thoracic surgery, history of paroxysmal AF, CHF, blood loss in surgery, HR, and MAP at ICU admission. As previous studies have identified, advanced age was associated with changes in ion channel conduction, contributing to intra-atrial conduction disorder.[53] Additionally, CHF may act synergistically with advanced age to increase the risk for POAF development.[53] Similarly, thoracic surgery,[54] HR,[46] atrial pressure,[55] and a history of paroxysmal AF[56] have been implicated in POAF development. Blood loss during surgery may increase oxidative stress and cause sympathetic/parasympathetic activation, resulting in POAF. Actually, ECG examination plays a vital role in AF detection.[57] Interatrial block and P wave parameters are other confirmed risk factors for AF,[58] which was different from our study. Previous research has focused on patients with an acute ischemic stroke rather than postoperative patients, who might have a different trigger of AF and experience fewer cardiovascular events before surgery.

Our study was novel because we combined MR to establish a new nomogram for predicting POAF in critically ill patients following thoracic and general surgery. The predictive power of the new MR nomogram was compared to CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST scoring systems. The CHA2DS2-VASc score is widely used to predict stroke risk in patients with AF. Traditionally, persistent anticoagulation is indicated for patients with AF and a CHA2DS2-VASc score of 2. Nevertheless, recent studies have extended the CHA2DS2-VASc score to predict the incidence of POAF following cardiac surgery.[59–62] Patients with higher CHA2DS2-VASc scores are more likely to have AF.[24] The C2HEST score can predict AF in patients with previous ischemic stroke and stratify poststroke patients into different risk groups for incident AF.[23] However, for predicting AF among patients with end-stage renal disease, both score systems showed poor predictive value, with an AUC of approximately 0.6. However, this has not been extended to more populations.[63] Considering the effect of long-term LA enlargement on AF, De Vos et al have developed the HATCH score for AF prediction.[34] Tischer T. has shown a significant increase in the prevalence of AF with an increasing HATCH score.[64] Emren et al have found that the HATCH score presented a higher predictive ability with an AUC of 0.77 vs 0.71 for the CHA2DS2-VASc score in patients undergoing CABG surgery[65] but with a poor discriminative ability to predict POAF after cardiac surgery with an AUC of 0.57.[66] From the combination of variables with higher predictive value, including CHA2DS2-VASc and HATCH, a new risk system COM-AF involved a large cohort to predict AF, which presented an AUC of 0.78 vs CHA2DS2-VASc AUC of 0.76 and HATCH AUC of 0.70.[21] However, diverse screening score systems may have different capabilities in detecting unrevealed AF of various populations. These scoring systems have been mostly used to predict the occurrence of AF after cardiac surgery rather than noncardiac surgery. Stronati et al have found 4 independent predictors and established HART scores (including age, hypertension, thyroid dysfunction, and intermediate or high-risk surgery) for all types of noncardiac elective surgery.[22] They have recorded different surgical procedures and classified them as low, intermediate, or high-risk according to European guidelines.[67] That study differs from ours in that it focused on all candidates instead of critically ill patients. According to European guidelines, the majority of the population in our study experienced intermediate- or high-risk surgery, which was the reason why the HART scoring system showed limited predictive value for POAF in ICU.[67] Our study filled the gap in predicting AF in the ICU population. We demonstrated that our new MR nomogram had better predictive capacity for POAF in critically ill patients than CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST scoring systems, as supported by IDI, NRI, and DCA. Studies on POAF based on predictive analytics have rarely mentioned critically ill patients and explored the association of MR. Critically ill individual risk evaluation for developing incidents of POAF is important for decision-making in early primary prevention and detection of AF, which might be associated with better outcomes.[28] The novelty of our study is not only demonstrating a promising nomogram but contributing to the pathophysiologic mechanisms of POAF in postoperative critically ill patients.

There were some limitations in this study. First, it was a single-center study susceptible to bias from practices. The predictive value of the MR nomogram needs to be further assessed in a multicenter study. Second, although it has been reported that the morbidity of thoracic and general noncardiac surgery is high, our findings might limit the external validity, which should be addressed in future studies with an extended patient population. In addition, the quantitative data of MR were not recorded, which might have limited our exploration of the relationship between MR and POAF. Our future step will evaluate the effect of the quantitative assessment of MR in this cohort. Finally, we did not have a validation cohort to confirm the predictive ability of the MR nomogram; thus, the possibility of overfitting could not be excluded.

## Conclusion

In summary, MR was an independent risk factor for POAF in postoperative critically ill patients. Additionally, the MR nomogram was a better predictive model of POAF in our cohort than established scoring systems such as CHA2DS2-VASc, HATCH, COM-AF, HART, and C2HEST. These findings provide a basis for further investigations into the role of MR in the pathogenesis of POAF in critically ill patients.

## Abbreviations

POAF, Postoperative atrial fibrillation; ICU, Intensive care unit; MR, Mitral regurgitation; LV, Left ventricular; ECG, Electrocardiogram; AKI, Acute kidney injury; UCG, Ultrasonic cardiogram; TR, Tricuspid regurgitation; LA, Left atrium; LVEF, LV ejection fraction; APACHE II, Acute physiology and chronic health evaluation; SOFA, Sequential organ failure assessment; CHF, Congestive heart failure; HT, Hypertension; TIA, Transient ischemic attack; CHD, Coronary heart disease; COPD, Chronic obstructive pulmonary disease; DAGs, Directed acyclic graphs; IQR, Interquartile range; ROC, Receiver operator characteristic; AUC, Area under the ROC curve; CIs, Confidence intervals; IDI, Integrated discrimination improvement; NRI, Net reclassification improvement; DCA, Decision curve analysis; MAP, Mean arterial pressure.

## Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethic Approval

The original study as well as secondary analysis was approved by the Human Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (Beijing, China) (approval no. 2020-ke-236).

## Consent for Publication

Written informed consent was obtained from patients or their next of kin before patients participated in this study. Consent requirements were waived for patients who died at the scene and never reached the hospital and for participants without known legal representatives.

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## Disclosure

The authors report no conflicts of interest in this work.

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