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RESEARCH PAPER

Risk Factors for Prognosis after the Maze IV Procedure in Patients with Atrial Fibrillation Undergoing Valve Surgery

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Abstract

The present study evaluated risk factors related to persistent atrial fibrillation (AF) at discharge (AF-d) and recurrent atrial fibrillation (rAF) and all-cause death after the maze IV procedure. Two hundred nineteen patients (63 female, aged 52.5±8.8 years) with valve disease and persistent AF undergoing valve surgery and the maze IV procedure in our center between 2015 and 2016 were included. Baseline demographic and clinical data were obtained by review of medical records. The median follow-up period was 27 months (interquartile range 21–34 months) in our patient cohort. The primary end point was all-cause death. The secondary end point was AF-d or rAF. rAF is defined as AF recurrence at 3 months or later after the procedure. Twenty-eight patients (12.8%) died during follow-up. Multiple logistic regression analysis showed that thrombocytopenia, elevated serum total bilirubin level, a larger right atrium, AF-d, and rAF were independent determinants for all-cause death after the maze IV procedure after adjustment for age, sex, and clinical covariates, including New York Heart Association class III/IV disease, hypertension, and aortic regurgitation, while valvular disease duration and left atrial diameter greater than 80.5 mm were independent determinants for AF-d, and thrombocytopenia, elevated serum total bilirubin level, higher mean pulmonary artery pressure, and AF-d were independent predictors for rAF. In conclusion, thrombocytopenia, elevated serum total bilirubin level, an enlarged right atrium, AF-d, and rAF are independent predictors of all-cause death in patients undergoing the maze IV procedure.

Keywords: Atrial fibrillation; maze IV; valve disease; thrombocytopenia

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. It is important to convert this arrhythmia to sinus rhythm to alleviate symptoms, improve heart function, and most importantly reduce the risk of stroke [1]. The Cox maze III/IV procedure is the standard surgical intervention to treat patients with AF undergoing valve operations [2].

Performance of the Cox maze IV procedure is associated with increased long-term survival in patients with AF undergoing cardiac surgery; however, the 10-year survival was only 62% in follow-up for 10 years in a retrospective study. It is important to investigate which patients will most likely benefit from this procedure [3]. Previous

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studies demonstrated that patient age, disease course, early recurrence of AF, hypertension, and the type of valve disease are potential factors related to increased mortality after the Cox maze III/IV procedure, while the role of right ventricular remodeling remains elusive [4, 5]. The present study analyzed risk factors for AF at discharge (AF-d), recurrent AF (rAF; AF recurrence at 3 months or later after the procedure), and mid-term death in patients after the Cox maze IV procedure.

Methods

This retrospective analysis was performed in line with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the local ethics committee at the University of Central South University. Two hundred nineteen patients who underwent valve surgery and a concomitant Cox maze IV procedure between January 2015 and December 2016 in our institution were continuously included and analyzed. No patients were excluded. The data are anonymous, and the requirement for informed consent was therefore waived [6].

The Cox maze IV procedure with radiofrequency was conducted with a Cardioblate bipolar RF ablator (Medtronic, Parkway, MN, USA). This technique was described elsewhere in detail and has been demonstrated to create transmural and continuous lesions [7]. Briefly, the ablation lines in the left atrium aimed at encircling the two right pulmonary veins and two left pulmonary veins, closing the antrum (lines between the right and left pulmonary veins; also called box lesion), with or without isolating the left atrial appendage, and selectively ablating the left isthmus (line connecting the mitral valve and the box lesion) and the line connecting the box lesion and the left atrial appendage. The right atrium ablation lines were set as follows: two purse-string sutures were applied, one for intercaval lesion and one for isolation of the cavotricuspid isthmus in certain cases. Then, isolate the right atrial appendage and terminal crest [8].

Baseline demographic and clinical data were obtained by review of medical records. The median follow-up period was 27 months (interquartile range 21–34 months) in our patient cohort. The primary end point was all-cause death. The secondary end point was AF-d or rAF. Death was ascertained from the official household registration survey or from witness by family members.

A standard 12-lead ECG was performed for all patients before the operation and at discharge and at the end of follow-up. ECG monitoring was performed for 3–7 days before the operation in every case. At the end of follow-up, for patients with sinus rhythm in the 12-lead ECG, Holter monitoring were performed continuously for another 3 days. The rhythm was confirmed by two experienced physicians who were not aware of the procedure.

Echocardiographic examination was performed in the left lateral position with use of a Sequoia Acuson instrument (Siemens Medical Solution, Mountain View, CA, USA) with 2.5 and 3.5 MHz probes before the operation. Left atrial diameter and right atrial diameter were measured by planimetry in the focused apical four-chamber view at the end of the T wave on the ECG. Left ventricular ejection fraction was measured with the biplane Simpson method.

Statistical analysis was performed with IBM SPSS for Windows (version 25), the statistical software package R (The R Foundation; https://www.r-project.org), and EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA; https://www.empowerstats.net). Descriptive statistics of baseline characteristics were stratified by survival state, AF-d, and rAF. All data were first evaluated for a normal distribution by means of the Anderson-Darling test. Continuous variables are summarized as the mean±standard deviation. When the group data were not normally distributed or if the group variances were unequal, the Mann-Whitney *U* test was used. Categorical data are summarized as numbers and percentages. Comparisons were made with use of Fisher's exact test. $P<0.05$ was considered to be statistically significant.

For risk factor analyses for AF-d and r-AF, univariable logistic regression was used, including the factors analyzed in the former test if $P<0.10$. Odds ratios with 95% confidence intervals were calculated. For risk factor analyses for all-cause death, univariable Cox regression was used, including the factors analyzed in Table 1 if $P<0.10$. Hazard ratios with 95% confidence intervals were calculated. All multiple regression models were stratified by age and sex. Other variables included in the multiple

Table 1 Preoperative Baseline Clinical Characteristics, Laboratory Test Results, and ECG and Echocardiographic Results Between Groups.

Variable	Overall	Group		P
		Survivor	Nonsurvivor	
	N = 219	*N* = 191	*N* = 28	
Age (years)	52.5±8.8	52.0±8.4	55.9±10.9*	0.03
Female (*n*, %)	137 (62.56%)	123 (64.40%)	14 (50.0%)	0.142
Valvular disease duration (months)	94.5±101.1	88.6±96.8	134.6±120.5*	0.029
Body mass index (kg/m^2)	22.5±2.9	22.5±3.0	22.6±2.5	0.723
Hypertension (*n*, %)	23 (10.6%)	17 (9.0%)	6 (21.4%)*	0.045
Coronary artery disease (*n*, %)	11 (5.0%)	8 (4.2%)	3 (10.7%)	0.140
Smoking (*n*, %)	26 (11.9%)	21 (11.1%)	5 (17.9%)	0.327
Diabetes mellitus (*n*, %)	10 (4.6%)	8 (4.2%)	2 (7.1%)	0.507
NYHA class III/IV disease (*n*, %)	182 (87.9%)	160 (88.9%)	22 (81.5%)	0.208
Systolic blood pressure (mmHg)	115±17	114±17	119±21	0.174
Mitral stenosis (*n*, %)	179 (81.7%)	159 (83.3%)	20 (71.4%)	0.175
Mitral regurgitation (*n*, %)	154 (70.3%)	137 (71.7%)	17 (60.7%)	0.332
AS (*n*, %)	52 (23.8%)	44 (23.2%)	8 (28.6%)	0.379
Aortic regurgitation (*n*, %)	27 (12.3%)	20 (10.5%)	7 (25.0%)*	0.782
Rhythm at follow-up				0.013
Sinus rhythm (*n*, %)	147 (67.1%)	134 (70.2%)	13 (46.4%)	
rAF (*n*, %)	72 (32.9%)	57 (29.8%)	15 (53.6%)	
Rhythm at discharge				<0.001
Sinus rhythm (*n*, %)	146 (66.7%)	137 (71.7%)	9 (32.1%)	
AF (*n*, %)	73 (33.3%)	54 (28.3%)	19 (67.8%)*	
White blood cells (10^9/L)	6.8±2.9	6.8±2.8	6.5±3.0	0.596
Neutrophils (10^9/L)	4.5±2.8	4.5±2.8	4.3±2.6	0.708
Mononuclear cells (10^9/L)	0.4±0.2	0.4±0.19	0.38±0.13	0.541
Hemoglobin (g/L)	128±21	128±20	123±30	0.217
MCV (%)	88.2±15.9	88.0±16.2	89.8±13.6	0.618
Platelets (10^9/L)	181±51	184±51	159±47*	0.023
ALT (U/L)	27.9±24.4	28.0±23.1	27.5±32.8	0.921
AST (U/L)	31.0±28.8	30.5±28.4	35.1±31.2	0.469
Albumin (g/L)	37.9±4.0	38.1±4.0	36.9±4.0	0.211
Total bilirubin (μmol/L)	16.1±7.7	15.7±7.5	19.0±8.6*	0.007
BUN (mmol/L)	6.8±2.5	6.6±2.4	7.6±3.0	0.071
Ccr (mL/min)	85.2±26.8	86.2±26.7	76.3±27.6	0.076
UA (μmol/L)	381±127	380±128	389±126	0.552
BNP (pg/mL)	323±345	299±280	505±638	0.262
CRP (mg/L)	13.9±27.0	12.3±23.9	25.6±42.2*	0.87
ASO (IU/mL)	66.1±48.5	64.2±48.7	84.5±43.4	0.992
INR	1.2±0.5	1.2±0.6	1.2±0.5	0.913
Heart rate (bpm)	87±22	87±22	88±24	0.416
QTc interval (ms)	448±41	447±42	455±39	0.338
QRS interval (ms)	89±18	88±17	93±20	0.154
LVEDD (mm)	50.4±8.7	50.1±8.5	52.3±10.2	0.202
Ejection fraction (%)	62.0±9.4	62.4±9.3	59.5±10.4	0.135
LAD (mm)	68.7±21.1	67.6±18.9	76.4±32.2*	0.021

Table 1 (continued)

Variable	Overall	Group		P
		Survivor	Nonsurvivor	
	N = 219	*N* = 191	*N* = 28	
RVD (mm)	38.2±6.3	38.0±6.2	40.0±7.2	0.12
RAD (mm)	39.5±7.9	39.1±7.8	42.8±8.2*	0.02
MPAP (mmHg)	33.3±5.2	33.1±4.9	34.7±6.7	0.144
Duration of aorta occlusion (min)	54.7±24.6	54.2±24.2	57.7±27.7	0.643
Cardiopulmonary bypass duration (min)	93.4±30.7	92.6±29.8	98.9±36.8	0.320
Valve prosthesis				0.715
Bioprosthetic valve	40 (19.8%)	35 (19.4%)	5 (22.7%)	
Mechanical valve prosthesis	162 (80.2%)	145 (80.6%)	17 (77.3%)	
INR after anticoagulation	2.0±0.8	2.0±0.8	2.1±0.6	0.378

Data are presented as the number and the percentage or the mean±standard deviation.
AF, atrial fibrillation; ALT, alanine aminotransferase; AS, aortic stenosis; ASO, anti-streptolysin O; AST, aspartate aminotransferase; BNP, brain-type natriuretic peptide; BUN, blood urea nitrogen; CCr, creatinine clearance; CRP, C-reactive protein; INR, international normalized ratio; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; MCV, mean corpuscular volume; MPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; QTc interval, corrected QT interval; RAD, right atrial diameter; rAF, recurrent atrial fibrillation; RVD, right ventricular diameter; UA, uric acid.
*Compared with survivor group, P<0.05.

regression analysis were valvular disease duration, hypertension, mitral stenosis, aortic regurgitation, platelet count, serum total bilirubin level, blood urea nitrogen level, C-reactive protein (CRP) level, left atrial diameter, right atrial diameter, and mean pulmonary artery pressure (MPAP) because their P values were less than 0.05 in the univariable analysis. Both age- and sex-adjusted analysis (model I) and age-, sex-, and clinical covariate–adjusted analysis (model II) were used to evaluate the impact of each variable on the risk of all-cause death. The clinical covariates included in the model were New York Heat Association (NYHA) association functional class III or class IV disease, hypertension, and aortic regurgitation. The criteria for inclusion in the model and removal from the model were significance levels less than 0.10, respectively. A two-tailed P value less than 0.05 was considered to be statistically significant.

Results

Twenty-eight patients (12.8%) died (nonsurvivor group) and 191 patients remained alive (survivor group) during follow-up. As shown in Table 1, the frequency of hypertension was significantly higher, the disease course was longer, and patients were older in the nonsurvivor group than in the survivor group. The type of valve disease was similar between the two groups, except for higher prevalence of aortic regurgitation in the nonsurvivor group. The prevalence of AF-d (67.8% vs. 28.3%, P<0.001) and that of rAF (53.6% vs. 29.8%, P=0.013) were significantly higher in the nonsurvivor group than in the survivor group.

Patients were older (54.8±8.8 years vs. 51.4±8.6 years, P=0.006) and the disease course was longer (118.2±104.7 months vs. 82.7±97.4 months, P=0.015) in the AF-d group than in the sinus rhythm group. Mortality was significantly higher in the AF-d group than in the sinus rhythm group (26.0% vs. 6.2%, P<0.001), and the frequency of rAF was also significantly higher in the AF-d group than in the sinus rhythm group (57.5% vs. 20.5%, P<0.001). The type of valve disease was similar between these two groups, except the frequency of comorbidity with aortic stenosis (AS) was higher in the AF-d group than in the sinus rhythm group at discharge (31.9% vs. 19.9%, P=0.049) (Supplemental Table 1).

Patients were older (54.4±8.5 years vs. 51.6±8.8 years, P=0.026) and mortality was significantly higher (20.8% vs. 8.8%, P=0.013) in the rAF group than in the sinus rhythm group. Other clinical variables, including type of valve disease, sex, disease course, body mass index, hypertension, coronary artery disease, myocardial infarction, smoking, proportion of NYHA class III/IV disease, and systolic blood pressure were similar between the two groups (Supplemental Table 2).

As shown in Table 1, the platelet count was significantly lower, while serum total bilirubin concertation and CRP concentration were significantly higher in the nonsurvivor group than in the survivor group. The white blood cell count was lower in the AF-d group than in the sinus rhythm group [$(6.1\pm2.1)\times10^9$/L vs. $(7.1\pm3.1)\times10^9$/L, P=0.025] (Supplemental Table 1). The platelet count was lower [$(167\pm49)\times10^9$/L vs. $(188\pm51)\times10^9$/L, P=0.004] and the serum total bilirubin concentration (18.3±8.7 μmol/L vs. 15.1±7.0 μmol/L, P=0.04) and the BUN concentration (7.4±2.8 mL/min vs. 6.5±2.4 mL/min, P=0.021) were higher in the rAF group than in the sinus rhythm group (Supplemental Table 2).

ECG parameters, including heart rate, corrected QT interval, and QRS interval were similar between the survivor group and the nonsurvivor group. The left atrium and right atrium were significantly larger in the nonsurvivor group than in the survivor group (Table 1).

ECG variables were similar between the AF-d group and the sinus rhythm group. Left atrial diameter (74.3±23.7 mm vs. 65.9±19.3 mm, P=0.005) and right atrial diameter (41.1±8.3 mm vs. 38.8±7.7 mm, P=0.04) were significantly larger in the AF-d group than in the sinus rhythm group (Supplemental Table 1).

Left atrial diameter (71.8±21.9 mm vs. 67.2±20.7 mm, P=0.129) was similar between the rAF group and the sinus rhythm group. Right ventricular diameter (39.5±6.8 mm vs. 37.6±6.0mm, P=0.035) and right atrial diameter (41.1±8.2 mm vs. 38.8±7.7 mm, P=0.040) were significantly greater and MPAP (34.5±5.4 mmHg vs. 32.8±5.0 mmHg, P=0.017) was significantly higher in the rAF group than in the sinus rhythm group (Supplemental Table 2).

Risk Factors for All-Cause Death

The variables with P<0.1 were included in univariable Cox regression (Table 2). Valvular disease duration, hypertension, aortic regurgitation, platelet count, serum total bilirubin concentration, CRP concentration, left atrial diameter, right atrial diameter, AF-d, and rAF were candidate determinants for lower overall survival in this cohort. Platelet count was a candidate determinant for greater overall survival in this cohort.

Multivariable models (Table 3) were established after adjustment for age and sex (model I) and after adjustment for age, sex, and clinical covariates (NYHA class III/IV disease, hypertension, and aortic regurgitation; model II). After adjustment for age and sex, valvular disease duration, thrombocytopenia, defined as platelet count less than 150×10^9/L, serum total bilirubin concentration, left atrial diameter, right atrial diameter, AF-d, and rAF remained as independent predictors of all-cause death (Table 3). After adjustment for age, sex, and clinical covariates, valvular disease duration, thrombocytopenia, serum total bilirubin concentration, right arterial diameter, and AF-d were found to be independent determinants for increased risk of all-cause death after the maze IV procedure in this cohort. The cutoff values for valvular disease duration, left atrial diameter, and right atrial diameter for determining adverse events were derived from receiver operating characteristic curve analysis and maximization of the sum of the sensitivity and specificity.

As shown in Figure 1A, all-cause mortality was 5.7% in patients with none of the five determinants (long valvular disease duration, thrombocytopenia, elevated serum total bilirubin concentration, large right atrial diameter and AF-d), 4.4% in patients with one determinant, 14% in patients with two determinants, 23.8% in patients with three determinants, and 66.7% in patients with four or five determinants (P<0.001 among groups).

Risk Factors for Persistent Atrial Fibrillation at Discharge

Valvular disease duration, coronary artery disease, left atrial diameter, and right atrial diameter were determinants for AF-d, while white blood cell count was a determinant for less AF-d (Table 2).

Valvular disease duration and left atrial diameter remained as determinants for AF-d after adjustment for age and sex in model I. After adjustment for age, sex, and clinical covariates (model II), valvular disease duration and left atrial diameter greater than 80.5 mm were the independent determinants for AF-d (Table 4).

As shown in Figure 1B, the AF-d rate was 27.8% in patients with neither of the two determinants (long valvular disease duration and large left atrial diameter), 34.8% in patients with one determinant,

Table 2 Univariable Regression for All-Cause Death, Atrial Fibrillation (Af) Recurrence, and Persistent Af at Discharge.

Variable	All-cause death (Cox regression)			Persistent AF at discharge			AF recurrence		
	HR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Valvular disease duration	1.003	1.000–1.006	0.026	1.003	1.001–1.006	0.017	1.002	0.999–1.004	0.273
Hypertension	2.522	1.023–6.221	0.045	1.306	0.537–3.178	0.556	1.083	0.437–2.688	0.863
SBP	1.016	0.995–1.038	0.136	1.015	0.999–1.032	0.069	1.006	0.989–1.002	0.502
Coronary artery disease	2.800	0.845–9.277	0.092	3.765	1.065–13.31	0.040	0.755	0.194–2.937	0.686
Mitral stenosis	0.518	0.228–1.177	0.116	0.799	0.392–1.629	0.537	1.590	0.729–3.465	0.244
Aortic regurgitation	2.489	1.058–5.857	0.037	1.442	0.632–3.290	0.385	1.476	0.647–3.371	0.355
White blood cell count	0.963	0.833–1.114	0.615	0.87	0.768–0.987	0.030	1.038	0.943–1.142	0.450
Neutrophil count	0.976	0.847–1.125	0.741	0.892	0.788–1.009	0.068	1.058	0.961–1.165	0.250
Platelet count	0.990	0.982–0.998	0.016	0.996	0.991–1.002	0.206	0.991	0.985–0.997	0.005
Thrombocytopenia	2.825	1.344–5.939	0.006	1.135	0.621–2.075	0.680	2.974	1.631–5.423	0.000
Total bilirubin	1.044	1.002–1.088	0.039	1.027	0.991–1.065	0.148	1.055	1.016–1.094	0.005
Total bilirubin >17.1 μmol/L	2.346	1.037–5.309	0.041	1.314	0.735–2.351	0.357	1.867	1.044–3.338	0.035
BUN	1.121	0.989–1.270	0.075	0.997	0.891–1.115	0.959	1.138	1.018–1.273	0.024
CCr	0.983	0.962–1.004	0.109	0.999	0.988–1.011	0.887	0.989	0.976–1.002	0.098
Uric acid	1.001	0.998–1.003	0.729	0.999	0.997–1.002	0.659	1.002	1.000–1.004	0.103
CRP	1.012	1.002–1.022	0.020	0.997	0.986–1.009	0.660	0.993	0.981–1.006	0.304
LAD	1.015	1.000–1.030	0.046	1.019	1.005–1.033	0.007	1.010	0.997–1.024	0.132
RAD	1.042	1.007–1.080	0.020	1.037	1.001–1.074	0.044	1.036	1.000–1.073	0.050
RVD	1.039	0.989–1.092	0.131	1.031	0.987–1.007	0.172	1.048	1.003–1.095	0.038
MPAP	1.052	0.985–1.124	0.128	1.010	0.957–1.006	0.714	1.067	1.011–1.126	0.019
AF-d	4.789	2.165–10.59	0.000				5.239	2.836–9.677	0.000
rAF	2.556	1.216–5.373	0.013						
Duration of aorta occlusion	1.006	0.990–1.021	0.489	1.009	0.997–1.021	0.127	0.997	0.986–1.009	0.675
Cardiopulmonary bypass duration	1.006	0.994–1.019	0.320	1.008	0.999–1.017	0.083	0.997	0.988–1.007	0.561
Valve prosthesis	0.821	0.283–2.377	0.716	0.670	0.328–1.369	0.272	0.744	0.362–1.531	0.422
INR after anticoagulation	1.075	0.641–1.803	0.784	0.808	0.532–1.227	0.317	0.915	0.618–1.355	0.658

AF-d, AF at discharge; BUN, blood urea nitrogen; CCr, creatinine clearance; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; INR, international normalized ratio; LAD, left atrial diameter; MPAP, mean pulmonary artery pressure; OR, odds ratio; RAD, right atrial diameter; rAF, recurrent AF; RVD, right ventricular diameter; SBP, systolic blood pressure.

Table 3 Multivariable Logistic Regression for All-Cause Death in Different Confounder Models.

Variable	Model I				Model II			
	Age- and sex-adjusted OR	95% CI		P	Age-, sex-, and clinical covariate–adjusted OR	95% CI		P
Valvular disease duration	1.004	1.000	1.007	0.039	1.005	1.001	1.009	0.007
Platelet count	0.991	0.982	1.000	0.056	0.99	0.981	1.000	0.043
Thrombocytopenia	2.550	1.104	5.890	0.028	2.444	1.036	5.763	0.041
Total bilirubin	1.046	0.996	1.098	0.071	1.042	0.989	1.098	0.120
Total bilirubin >17.1 μmol/L	2.344	1.019	5.391	0.045	2.482	1.028	5.996	0.043
LAD	1.023	1.004	1.042	0.018	1.017	0.998	1.036	0.084
LAD >80.5 mm	2.746	1.188	6.348	0.018	2.350	0.976	5.660	0.057
RAD	1.045	1.000	1.093	0.052	1.053	1.006	1.102	0.028
RAD >45.5 mm	3.412	1.415	8.230	0.006	4.189	1.638	10.71	0.003
AF-d	4.799	2.017	11.42	0.000	5.975	2.4	14.87	0.000
rAF	2.437	1.076	5.518	0.033	2.293	0.986	5.334	0.054

The clinical covariates were New York Heart Association functional class III or class IV disease, hypertension, and aortic regurgitation. Thrombocytopenia is defined as a platelet count less than 150×10^9/L.
AF-d, atrial fibrillation at discharge; CI, confidence interval; LAD, left atrial diameter; OR, odds ratio; RAD, right atrial diameter; rAF, recurrent atrial fibrillation.

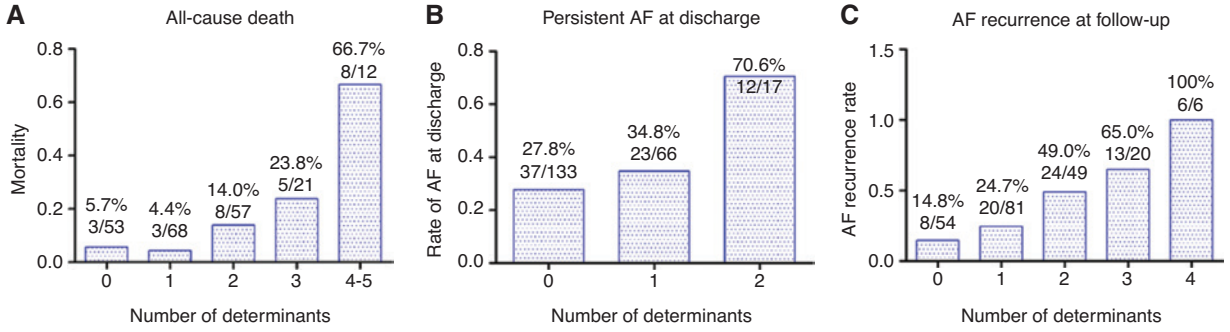

Figure 1 The Association between Number of Determinants and Clinical Outcomes.
(A) Frequency of all-cause death in patients with none, one, two, three, or four or five of the determinants of death demonstrated in this study, including long valvular disease duration, thrombocytopenia, elevated serum total bilirubin concentration, large right atrial diameter, and persistent atrial fibrillation (AF) at discharge. P<0.001 among groups. (B) Frequency of persistent AF at discharge in patients with none, one, or both of the determinants demonstrated in this study (i.e., long valvular disease duration and large left atrial diameter). P=0.002 among groups. (C) Frequency of AF recurrence at follow-up in patients with none, one, two, three, or all four of the determinants demonstrated in this study (i.e., thrombocytopenia, elevated total bilirubin concentration, high MPAP and AF at discharge). P<0.001 among groups.

and 70.6% in patients with both determinants (P=0.002 among groups).

Risk Factors for Atrial Fibrillation Recurrence at Follow-up

On the other hand, baseline thrombocytopenia, serum total bilirubin concentration, BUN concentration, right atrial diameter, right ventricular diameter, MPAP, and AF-d were potential candidate determinants for rAF in univariable logistic regression (Table 2).

Table 5 shows the multiple logistic analysis results for rAF. Thrombocytopenia, total bilirubin concentration, BUN concentration, high MPAP and AF-d remained as candidate determinants of rAF. After adjustment for age, sex, and clinical covariates (model II), thrombocytopenia, total bilirubin

Table 4 Multivariable Logistic Regression for Persistent Atrial Fibrillation at Discharge in Different Confounder Models.

Variable	Model I				Model II			
	Age- and sex-adjusted OR	95% CI		P	Age-, sex-, and clinical covariate–adjusted OR	95% CI		P
Valvular disease duration	1.003	1.000	1.006	0.026	1.003	1.000	1.006	0.023
White blood cell count	0.884	0.778	1.004	0.058	0.878	0.768	1.003	0.055
Neutrophil count	0.901	0.795	1.021	0.101	0.892	0.781	1.018	0.089
LAD	1.023	1.008	1.037	0.002	1.025	1.010	1.040	0.001
LAD >80.5 mm	1.933	1.014	3.686	0.045	1.995	1.027	3.873	0.041

The clinical covariates were New York Heart Association functional class III or class IV disease, hypertension, and aortic regurgitation.
CI, confidence interval; LAD, left atrial diameter; OR, odds ratio.

Table 5 Multivariable Logistic Regression for Recurrence of Atrial Fibrillation in Different Confounder Models.

Variable	Model I				Model II			
	Age- and sex-adjusted OR	95% CI		P	Age-, sex-, and clinical covariate–adjusted OR	95% CI		P
Thrombocytopenia	2.687	1.45	4.979	0.002	3.103	1.631	5.906	0.001
Platelet count	0.992	0.986	0.999	0.016	0.99	0.983	0.997	0.003
Total bilirubin	1.053	1.014	1.093	0.007	1.055	1.015	1.097	0.007
Total bilirubin >17.1 μmol/L	1.882	1.045	3.387	0.035	1.989	1.087	3.637	0.026
BUN	1.121	1.015	1.256	0.050	1.118	0.996	1.256	0.058
AF-d	4.898	2.631	9.116	0.000	5.048	2.663	9.571	0.000
MPAP	1.085	1.025	1.148	0.005	1.088	1.027	1.154	0.004
MPAP >36 mmHg	1.976	1.025	3.807	0.042	2.266	1.143	4.493	0.019

The clinical covariates were New York Heart Association functional class III or class IV disease, hypertension, and aortic regurgitation. Thrombocytopenia was defined as a platelet count less than 150×10^9/L.
AF-d, arial fibrillation at discharge; BUN, blood urea nitrogen; CI, confidence interval; MPAP, mean pulmonary artery pressure; OR, odds ratio.

concentration, AF-d, and MPAP or MPAP greater than 36 mmHg remained as independent predictors of rAF.

As shown in Figure 1C, the rAF rate was 16.4% in patients with none of the four determinants (i.e., thrombocytopenia, elevated total bilirubin concentration, high MPAP, and AF at discharge), 25.6% in patients with one determinant, 59.2% in patients with two determinants, 65.0% in patients with three determinants, and 100% in patients with all four determinants ($P<0.001$ among groups).

Discussion

The major findings of the present study are as follows:

1. Besides AF-d and rAF, valvular disease duration, thrombocytopenia, elevated serum total bilirubin concentration, and right atrial diameter are additional determinants of increased mid-term all-cause mortality in patients undergoing valve surgery and the maze IV procedure.

2. AF-d was associated with higher mortality and higher risk of rAF. Valvular disease duration and left atrial diameter are major determinants of AF-d.
3. Thrombocytopenia, elevated serum total bilirubin concentration, AF-d, and MPAP are independent predictors of rAF.
4. The risk of death and rAF increased with increase in the number of the defined independent predictors in this patient cohort.

Around 20 cardiac surgery risk scores are available now [9] but none of them was developed to specifically evaluate the postprocedural outcome for patients undergoing the maze IV operation. Exploration of additional risk factors related to survival and rhythm outcome might allow improved therapy strategies for patients with AF intended to be treated with valve surgery and the maze procedure. In this study, in line with previous reports [4, 7, 10–13], we report that AF at discharge and/or during follow-up is related to lower survival in this patient cohort. Moreover, we find that thrombocytopenia, elevated serum total bilirubin concentration and right atrial diameter greater than 45.5 mm are additional determinants of increased mid-term all-cause death in these patients. To the best of our knowledge, this is the first report describing the impact of these additional risk factors on the outcome of patients after valve surgery and the maze IV procedure.

Wei et al. [14] found that platelet counts could predict in-hospital all-cause mortality for patients with rheumatic heart disease undergoing valve replacement surgery both with and without previous AF. One-year survival was significantly lower in patients with thrombocytopenia compared with controls. In addition, thrombocytopenia was an independent predictor of postoperative 1-year all-cause mortality. In line with their results, our observation indicates that thrombocytopenia is linked to worse survival outcome and increased risk of rAF during follow-up in this patient cohort, suggesting a strong predictive role of thrombocytopenia for the outcome of patients after valve surgery and the maze IV procedure. Multiple underlying reasons were postulated to explain the link between thrombocytopenia and worse outcome after valve surgery [14], and it was proposed that thrombocytopenia might reflect severer right-sided heart failure and abnormal hemodynamics (related to hepatic congestion and resultant hypersplenism) [15]. Indeed, our results demonstrated that an enlarged right atrium serves as another determinant for worse survival outcome after the maze IV procedure.

Most studies suggested that cardiac surgery using cardiopulmonary bypass might result in hyperbilirubinemia, a multifactorial process caused by both impaired liver function of bilirubin transport and increased production of bilirubin because of hemolysis. Postoperative hyperbilirubinemia is a known predictor of worse outcome after cardiac surgery [16]. Studies also showed that preoperative hyperbilirubinemia was an independent predictor of postoperative hyperbilirubinemia and postoperative death [17, 18]. In line with the above findings, we found that preoperative total bilirubin level is an independent risk factor for worse survival outcome and rAF after valve surgery and the maze procedure. A previous study found that serum bilirubin was significantly associated with high pulmonary artery pressure [19], while we also showed that elevated MPAP is an independent risk factor for rAF, and thus the interactive link between preoperative and postoperative hyperbilirubinemia and MPAP might significantly affect the outcome of patients undergoing valve surgery and the maze procedure.

Our study showed that larger right atrial diameter served as an independent risk factor for worse outcome in this patient cohort. This finding is in line with that of a previous report where that preoperative right atrial diameter was an independent predictor of ablation failure in patients undergoing surgical ablation during concomitant cardiac surgery [5].

Longer valvular disease duration was found to be an independent risk factor for AF-d and worse outcome and larger left atrial diameter served as a risk factor for AF-d; the underlying reasons are straightforward and were clarified by previous studies [7, 20].

Our results highlight the clinical importance to restore sinus rhythm in this patient cohort and strategies to control or modulate preoperative and postoperative total bilirubin level and platelet count,

and that left/right atrial reconstruction might possibly affect the rhythm and survival outcome after the procedure. Perioperative diuretic use aiming to improve right ventricular function and reduce MPAP might be a crucial option to improve the outcome of patients undergoing valve surgery and the maze procedure [21].

In conclusion, besides AF-d and rAF, thrombocytopenia, elevated serum total bilirubin concentration, and an enlarged right atrium are independent predictors of all-cause death in patients undergoing valve surgery and the maze IV procedure. Controlling these risk factors might contribute to further improvement of outcome in these patients. Prospective studies are warranted to validate if the defined outcome determinants in this study could be used for risk stratification of patients undergoing valve surgery and the maze procedure.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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