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Risk Factors for Embolism in Cardiac Myxoma: A Retrospective Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E 1 Deng-ke He*
G 1 Yu-feng Zhang*
C 1 Yin Liang*
B 2 Shi-xing Ye
D 3 Chong Wang
F 1 Bo Kang
A 1 Zhi-nong Wang

1 Department of Cardiothoracic Surgery, Changzheng Hospital, Second Military Medical University, Shanghai, P.R. China
2 Department of Cardiothoracic Surgery, Fuzhou General Hospital, Fuzhou, Fujian, P.R. China
3 Department of Cardiothoracic Surgery, Changhai Hospital, Second Military Medical University, Shanghai, P.R. China

* These authors contributed equally to this paper

Corresponding Author: Zhinong Wang, e-mail: wangzn007@163.com

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Background: Myxomas are the most common primary heart tumors and are closely associated with embolic events. Cardiac myxomas typically arise from the interatrial septum at the border of the fossa ovalis in the left atrium. Any other location is considered atypical. Embolism, one of the complications of myxoma, is associated with high morbidity and mortality. The aim of this study was to investigate the risk factors for embolism in patients with cardiac myxoma.

Material/Methods: In this retrospective study, a cohort of 162 patients with cardiac myxomas was surgically treated between January 1998 and June 2014 at 3 cardiac centers in China. Preoperative data, including platelet count, sex, age, and the tumor (size, location, surface, and attachment), were compared between embolic and non-embolic groups of patients.

Results: No significant differences in vascular risk factors were seen between the 2 groups. However, the percentage of higher platelet count (>300×10^9/L) and mean platelet volume in the embolic group were significantly higher than in the non-embolic group (P=0.0356, and 0.0113, respectively). Irregular surface and atypical location of the myxomas were also independently associated with increased risk of embolic complications.

Conclusions: Tumor location, macroscopic appearance, mean platelet volume, and high platelet count are strong risk factors for embolic events in patients with cardiac myxomas.

MeSH Keywords: Embolism • Heart Neoplasms • Myxoma

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Background

Atrial myxomas are the most common primary heart tumors. Primary tumors of the heart are uncommon, with an incidence ranging between 0.0017% and 0.19% and accounting for nearly half of all benign heart tumors [1,2]. Cardiac myxomas are found in any of the 4 cardiac chambers, with the majority occurring in the left atrium arising in the interatrial septum at the border of the fossa ovalis [3–6]. Cardiac myxomas are initially diagnosed using echocardiography, computed tomography, and magnetic resonance imaging to determine their location, site of pedicle attachment, and size (Figure 1A, 1B). Two-dimensional echocardiography is the diagnostic procedure of choice. Pathological examination is needed for the final diagnosis.

Embolism is a major complication occurring in 30–50% of patients with cardiac myxomas, and is closely associated with cardiac mortality, especially preoperative [7,8]. Despite prompt thrombolytic therapy or embolectomy, sequelae of embolism still remain. Surgical removal is the most effective therapeutic and preventive intervention in cardiac myxoma. However, the specific risk factors contributing to embolism in cardiac myxomas are still unclear. In this retrospective study, we analyzed the clinical data at 3 centers in China over a 16-year period to determine the risk factors of embolism in patients with cardiac myxomas (Figure 1C, 1D).

Material and Methods

Patients

This is a retrospective study of 162 patients with cardiac myxomas surgically treated between January 1998 and June 2014 at Changzheng Hospital, Changhai Hospital, and Fuzhou General Hospital, in China. Patients with blood diseases prone to thrombosis and those with a history of thrombus were excluded. The diagnosis of cardiac myxomas was confirmed by postoperative pathological examination. This study was approved by our Institutional Review Board.

Surgery

The surgical excision of myxoma was performed under the following conditions: 1) Medial sternotomy to open the chest, followed by pericardial incision; 2) Cannulation of caval veins and aorta to establish the bypass system; 3) Moderate hypothermia and cardioplegia using warm blood crystalloids to achieve heart arrest; 4) Partial resection of the endocardium around the tumor base for tumor excision; 5) Avoidance of embolization of tumor fragments; and 6) Valve surgery if indicated by severe valvular regurgitation due to enlarged annulus.

Data collection

Based on clinical presentation and cranial computed tomography, patients were classified into embolic and non-embolic groups. Patients' clinical profile was retrieved, including sex, age, body

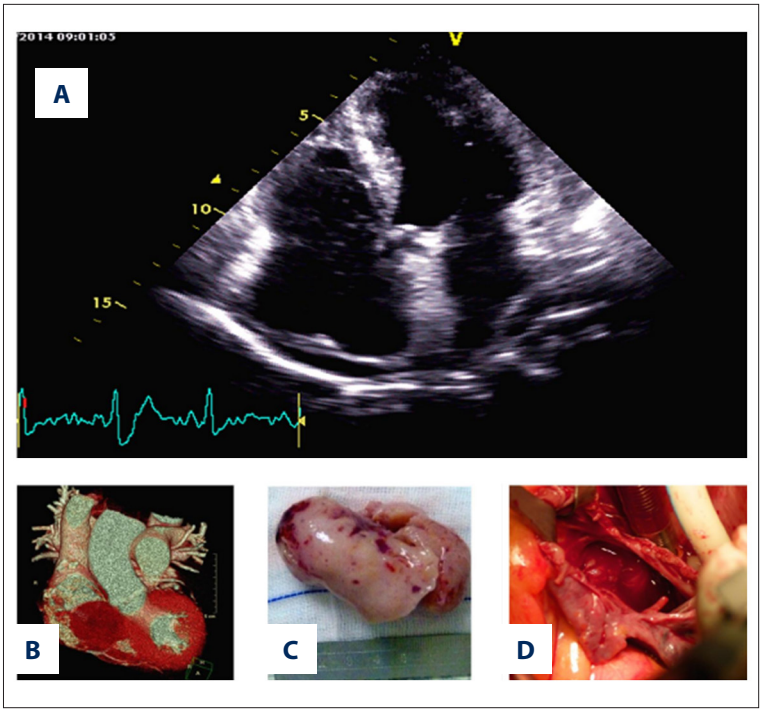

Figure 1. (**A**) Atrial myxoma seen in two-dimensional echocardiography. (**B**) Atrial myxoma diagnosed by three-dimensional reconstruction of spiral computed tomography. (**C**) Myxoma seen after removal. (**D**) Perioperative picture.

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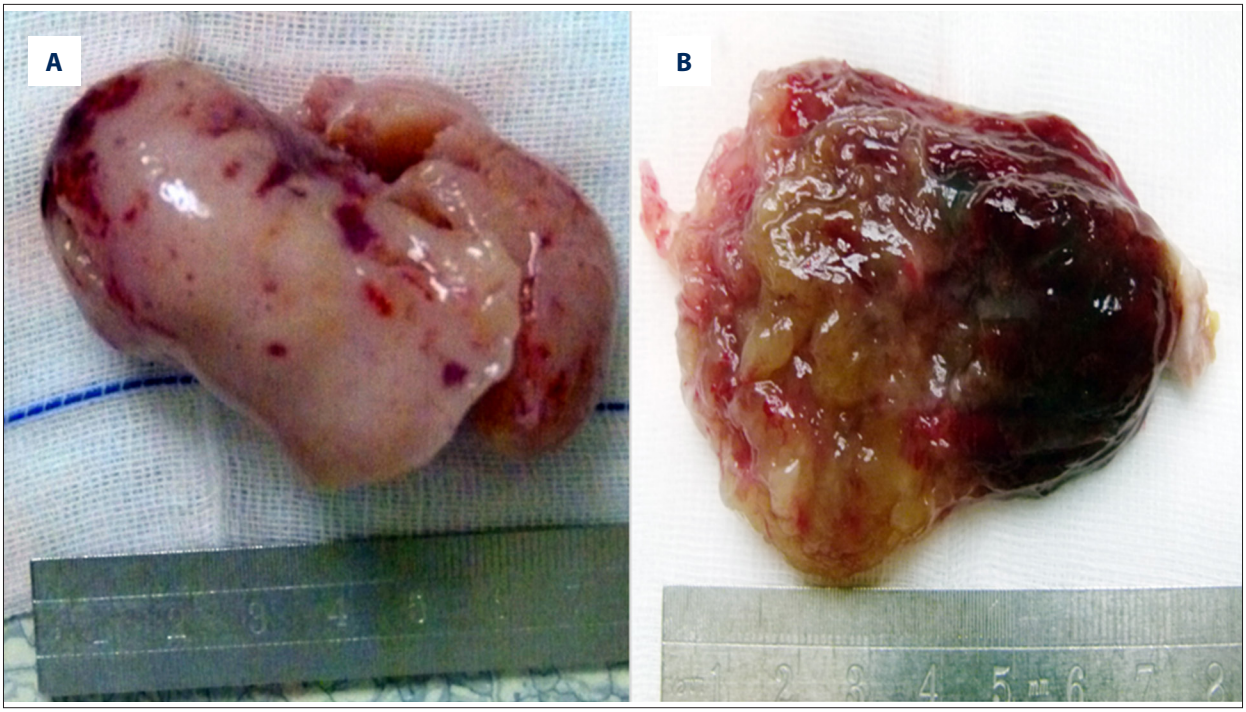

Figure 2. Two types of myxomatous surface. (**A**) Irregular or villous surface and soft consistency (irregular type). (**B**) Smooth surface and compact consistency (polypoid type).

surface area, body mass index, history of atrial fibrillation or flutter, concomitant valvular heart disease, pulmonary artery hypertension, coronary artery disease, blood coagulation function, intravascular ultrasound, and characteristic features of the myxomas (size, appearance, location, attachment). Typical myxomas arise from the interatrial septum at the border of the fossa ovalis in the left atrium. Atypical myxomas arise from other sites of the left atrium or in the other cardiac chambers [9]. Macroscopically, the surface of myxomas is classified into 2 types (Figure 2): the irregular type has a surface with a soft consistency and multiple exquisite villous extensions on the surface, and an irregular or villous surface; and the polypoid type has a compact consistency with polypoid appearance and smooth surface [7,10–12].

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). Continuous variables were reported as means (±SD) or median (range) as appropriate, and the Wilcoxon 2-sample test was used for comparisons. Categorical variables were described as frequencies and percentages, which were compared using chi-square test or Fisher's exact test. Binary logistic regression was used to identify the independent risk factors of embolic events and the multivariable model was built by stepwise selection. Candidate variables were carefully selected to satisfy the entry criterion of $P<0.10$ in the univariate analysis. A *P* value less than 0.05 was considered statistically significant.

Results

Patient characteristics

No significant differences in age, sex, body mass index, or other clinical characteristics were observed between the embolic and non-embolic groups (Table 1). All patients denied a family history of symptomatic cardiac myxomas. Over half of the patients (53.7%) were age 40–60 years. A preponderance of left atrial involvement was observed in 137 patients (84.6%), with 34.3 myxomas arising from the fossa ovalis. In addition, a prevalence of female sex was found (female/male ratio=2.6: 1). Our results are consistent with previous case studies involving populations from France, Germany, the United States, Austria, and Korea [6,13,14].

Clinical presentation

The embolic group included 33 patients (20.4%) and the non-embolic group included 129 patients (79.6%). Only 1 patient in our study presented both cerebral and peripheral embolism. The embolic group included 25 patients with cerebral infarction. Of these patients, 2 lost vision because of central retinal artery occlusion and 1 patient had internal carotid artery infarction. Six patients presented with pain and dysfunction of the lower extremities caused by acute aortic thrombosis, including 1 patient with aortic thrombus of the external iliac artery. One patient had pulmonary embolism and 1 patient had coronary thrombosis (Table 2).

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Table 1. Patient demographics.

	Embolic group (n=33)		Non-embolic group (n=129)		*P*-value
Age (year)	48	(IQR 38–61)	54	(IQR 46–63)	0.798
Female, n (%)	13	(32.5)	39	(30)	0.304
Body mass index, kg/m^2	21.0	(IQR 19.4–23.4)	21.7	(IQR 19.9–23.9)	0.222
Body surface area, m^2	1.6	(IQR 1.5–1.7)	1.6	(IQR 1.5–1.8)	0.068
Hypertension, n (%)	5	(15.15)	19	(14.73)	0.8986
New York Heart Association class, n (%)					0.1054
I	3	(9.09)	12	(9.30)	
II	19	(57.58)	47	(36.43)	
III	10	(30.30)	63	(48.84)	
IV	1	(3.03)	7	(5.43)	
Diabetes (n)	3	(9.09%)	6	(4.65%)	0.3897
Hyperlipidemia (n)	4	(12.12%)	7	(5.43%)	0.2368
Current smoking (n)	5	(15.15%)	9	(6.98%)	0.1635
Current drinking (n)	1	(3.03%)	2	(1.55%)	0.4975
Arrhythmia (n)	6	(20.69%)	14	(10.85%)	0.2480
Atrial fibrillation (n)	3	(10.35%)	9	(6.98%)	0.7110
Coronary artery disease (n)	1	(3.03%)	5	(3.88%)	1.0000
Pulmonary arterial hypertension (n)	2	(6.06%)	12	(9.30%)	1.0000
Valvular heart disease (n)	19	(57.6%)	77	(59.7%)	0.8447
Mitral Valvular heart disease (n)	18	(54.5%)	63	(48.8%)	0.6968
Tricuspid Valvular heart disease (n)	13	(39.4%)	63	(48.8%)	0.4347
Aortic Valvular heart disease (n)	2	(6.1%)	3	(2.3%)	0.2691

Values are n/total N (%), or median (interquartile range).

Among the 129 patients in the non-embolic group, chest pain and discomfort were the most common cardiac symptoms, observed in 79 patients (48.8%). Dyspnea, palpitation, and symptoms of acute heart failure occurred in 47, 36, and 14 patients, respectively. Notably, 1 of these patients presented with cerebral hemorrhage. Nineteen patients (18.6%) were asymptomatic and diagnosed with cardiac myxoma incidentally during examination for other conditions or during physical examination.

Laboratory results

The findings of echocardiography and hematological tests are listed in Table 3. There was no significant difference in platelet count between the 2 groups (250 [IQR 203–311] 10^9/L *vs.* 218 [IQR 182–273] 10^9/L, *P*=0.0724). The mean platelet volume (MPV) was significantly higher in the embolic group compared with the non-embolic group (10.9 fL [IQR 10.3–11.4 fL] *vs.* 10.40 fL [IQR 9.7–11.30 fL]; *P*=0.0384). No significant differences were found in the other hematological parameters between the 2 groups, including blood type, white blood cell count, and granulocyte count. The 2 groups did not differ significantly in echocardiographic parameters such as left atrial volume, left atrial volume index, and left ventricular ejection fraction (Table 3).

Histology and pathological data

Nearly two-thirds of irregular myxomas were found in the embolic group, but less than half in the non-embolic group. Ten cases presented with blood clots and 3 cases involved mucosubstance

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Table 2. Clinical presentation of cardiac myxoma.

Symptom	Patients, n (%)
Embolism	
Brain	25 (15.43)
Limb	6 (3.70)
Pulmonary	1 (0.62)
Coronary	1 (0.62)
Cardiac obstructive symptoms	
Dyspnea	47 (29.01)
Chest pain or discomfort	79 (48.77)
Palpitation	36 (22.22)
Dizziness or syncope	4 (2.47)
Symptom of acute heart failure	14 (8.64)
Constitutional symptoms	
Fatigue	4 (2.47)
Myalgia	1 (0.62)

Values are medians (interquartile range).

adhering to the surface. Round, stellate, or irregular tumor cells were found with myxoid or narrow fibrous matrix in the intercellular region. Eighteen cases showed deposits of hemosiderin and iron salts in the tumor center, 8 cases presented with spotty calcification, and 1 case with ossification. Nearly all the myxomas detected immunohistochemically were positive for Vimentin (46/50). Positivity for CD31 and CD34 was noted in 95.6% (43/45) and 90% (36/40) of cases, respectively (Figure 3).

Myxoma characteristics

There were no significant differences in the size of myxomas between the 2 groups (20 cm^2 [IQR 10–30 cm^2] *vs.* 18 cm^2 [IQR 10–25 cm^2]; *P*=0.3696; Table 4). However, significantly more patients in the embolic group had large myxomas (>25 mm^2) than in the non-embolic group (36.4% *vs.* 17.1%, *P*=0.0276). Tumor attachment did not differ significantly between the 2 groups (1.0 cm [IQR 0.8–1.5 cm] *vs.* 1.0 cm [IQR 0.5–1.3 cm]; *P*=0.1227]. Atypical myxomas were significantly higher in the embolic than in the non-embolic group (45.5% *vs.* 16.3%, *P*=0.0303). The irregular surface of myxomas was significantly more common in the embolic group compared with the non-embolic group (63.6% *vs.* 41.1%, P=0.0337).

Perioperative data

No significant differences were observed in perioperative comorbidity, blood products used, total chest tube loss, and operation time between the 2 groups. However, the ventilation time, CCU and total hospital stay were significantly longer in the embolic group compared with the non-embolic group (Table 5). Significantly decreased MPV levels and platelet counts were found after the surgical excision of myxomas in the 2 groups (Table 6).

Multivariate analysis

Table 7 shows the results of logistic regression analyses. Binary logistic regression revealed that the most important risk factor contributing to embolism was the platelet count higher than normal (odd ratio: 2.911; *P*=0.0356). Atypical location (odd ratio: 2.537; *P*=0.0477) and irregular surface (odd ratio:

Table 3. Echocardiographic and hematological parameters: embolic versus non-embolic groups.

	Embolic group (n=33)		Non-embolic group (n=129)		*P*-value
White blood cell count (10^3/mL)	6.43	(IQR 5.52–8.52)	6.70	(IQR 5.60–8.01)	0.9012
Neutrophil granulocytes (%)	67.4	(IQR 59.7–72.1)	63.7	(IQR 59.1–70.3)	0.4198
Platelet count (10^9/L)	250	(IQR 203–311)	218	(IQR 182–273)	0.0724
>300×10^9/L (n)	10	(30.3%)	18	(14.0%)	0.0273
MPV (fL)	10.9	(IQR 10.3–11.4)	10.40	(IQR 9.70–11.30)	0.0384
Prothrombin time (s)	14.2	(IQR 12.8–16.7)	13.5	(IQR 12.5–15.2)	0.1483
International normalized ratio	1.0	(IQR 1.0–1.1)	1.0	(IQR 1.0–1.1)	0.5749
Blood type O (n)	12	(36.4%)	33	(25.6%)	0.1547
Left atrial volume (ml)	69.2	(IQR 55–93)	70.4	(IQR 51–90)	0.8242
Left atrial volume index	47.1	(IQR 32.3–61)	43.7	(IQR 30.8–57)	0.4466
LVEF (%)	63	(IQR 57–65)	62.5	(IQR 57.4–65)	0.9152

Values are medians (interquartile range). LVEF – left ventricular ejection fraction; MPV – mean platelet volume.

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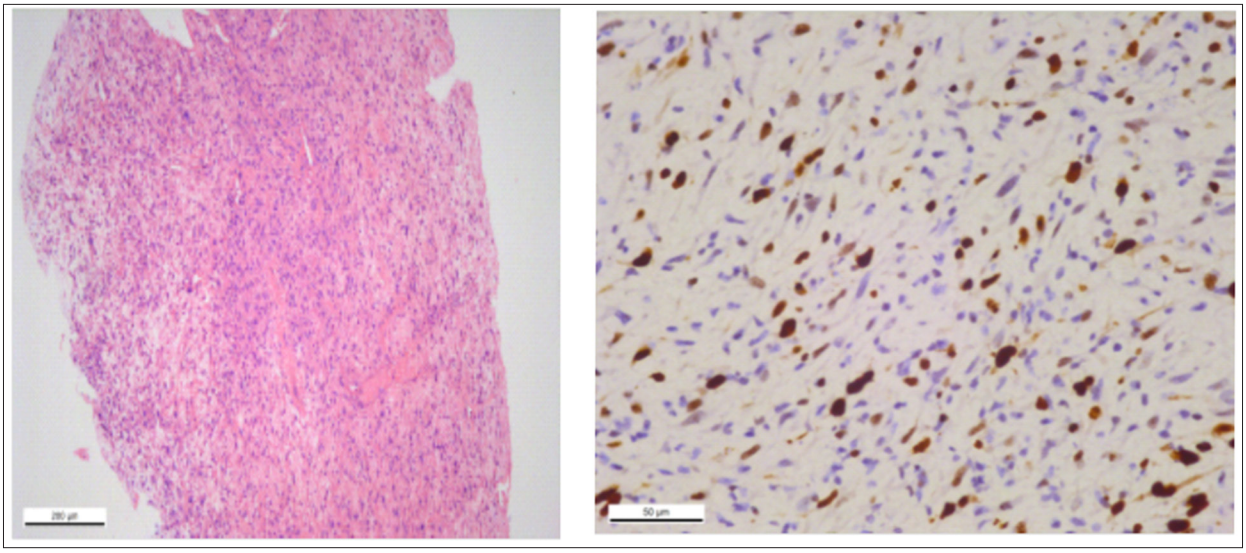

Figure 3. The histologic morphological observations and immunohistochemical staining of myxomas.

Table 4. Myxoma characteristics: embolic versus non-embolic groups.

	Embolic group (n=33)		Non-embolic group (n=129)		*P*-value
Size (cm^2)	20	(IQR 10–30)	18	(IQR 10–25)	0.3512
>25 cm^2 (n)	14	(36.4%)	30	(17.1%)	0.0276
Irregular surface (n)	21	(63.4%)	55	(41.1%)	0.0337
Attachment size (cm)	1.0	(IQR 0.8–1.5)	1.0	(IQR 0.5–1.3)	0.1227
>1 cm (n)	10	(30.3%)	33	(25.58%)	0.6594
Atypical location	15	(45.5%)	32	(16.3%)	0.0303

Values are n/total N (%), or median (interquartile range).

2.701; *P*=0.0216) of tumor was a significant predictor of embolic complications. MPV was an independent predictor of embolism (odds ratio [OR]: 1.468; 95% confidential interval [CI]: 1.062–2.027; *P*=0.02) (Table 7).

Discussion

Embolism in patients with cardiac myxomas is associated with tumor appearance, location, and mobility [10,12,15]. Consistent with established results reported in the literature, our study confirmed that surface of the myxoma was an important risk factor contributing to embolism (HR: 2.701; *P*=0.0216). Irregular surface contributes to tumor fragmentation and increased interactive areas, resulting in embolism.

Platelets play an important role in several thromboembolic events [16–18]. Mean platelet volume and platelet count are 2 important indices of hemostasis and dysfunction. It was reported previously that enlarged platelets were metabolically more active and reflect higher thrombogenic potential [19]. The high platelet count was found to be associated with an elevated risk of cancer-associated thrombosis [16,17]. However, their role in myxoma-related embolism is still uncertain. Our study found that MPV level and the platelet count also play an important role in the embolism of patients with cardiac myxoma. It has been shown that inflammatory cytokine levels were increased in patients with cardiac myxomas, which may stimulate the increased production of larger platelets [20,21]. The decrease in inflammatory cytokine levels after tumor removal reinforces this finding.

Infected myxomas in combination with emboli were reported to greatly elevate the risk for systemic embolization [12,22]. However, our study found no significant differences in white blood count and neutrophils between the embolic and non-embolic groups, probably due to the low sensitivity of the 2 parameters in distinguishing the infected myxomas from the others.

Tumor size and location are common echocardiographic parameters [10]. Biljana et al. reported that embolization in

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Table 5. Intraoperative and postoperative data.

	Embolic group (n=33)		Non-embolic group (n=129)		*P*-value
Perioperative data					
Cardiopulmonary bypass (min)	59	(IQR 47–72)	58	(IQR 49–76)	0.8369
C_x (min)	24	(IQR 18–35)	24	(IQR 18–35)	0.8875
Assistant time (min)	24	(IQR 20–29)	24	(IQR 17–29)	0.3448
Clinical outcomes					
All blood products used (mL/kg)	14.4	(IQR 0–26.2)	8	(IQR 0–21.5)	0.2843
PRBCs total, ml/kg	7.8	(IQR 0–13.6)	3.8	(IQR 0–11.9)	0.2092
Total chest tube loss (mL)	360	(IQR 180–520)	375	(IQR 235–540)	0.5057
Hospitalization					
Ventilation length (h)	20	(IQR 10–26)	13	(IQR 7–17)	0.0183
CCCU stay (days)	2	(IQR 2–4)	2	(IQR 1–3)	0.0436
Total hospital stay (days)	17	(IQR 14–21)	14	(IQR 11–17)	0.0002
Comorbidity					
SSI (n)	0	(0%)	0	(0%)	1.000
Renal dysfunction (n)	0	(0%)	1	(0.78%)	1.000
In-hospital mortality (n)	0	(0%)	0	(0%)	1.000

Values are medians (interquartile range). Cx – total aortic cross-clamp time; PRBC – packed red blood cells; CCCU – comprehensive cardiovascular care unit; SSI – surgical site infection.

Table 6. MPV and platelet count before and after surgical excision of myxomas.

	Pre		Post		P-value
MPV (fL)	10.50	(IQR 9.80–11.30)	9.60	(IQR 8.80–9.90)	<0.001
Embolic group	10.90	(IQR 10.30–11.40)	9.60	(IQR 9.00–10.10)	<0.001
Non-embolic group	10.40	(IQR 9.70–11.30)	9.60	(IQR 8.65–9.90)	<0.001
Platelet count (10^9/L)	227	(IQR 183–283)	128.5	(IQR 100–168)	<0.001
Embolic group	250	(IQR 203–311)	142	(IQR 109–172)	<0.001
Non-embolic group	218	(IQR 182–273)	128	(IQR 97–167)	<0.001
Platelet count >300×10^9/L (n)	28	(17.3%)	1	(0.6%)	<0.001
Embolic group	10	(30.3%)	0	(0%)	<0.001
Non-embolic group	18	(14.0%)	1	(0.8%)	<0.001

MPV – mean platelet volume; IQR – interquartile range.

patients with right atrial myxomas was more frequent [13]. In our study, we found it very interesting that the atypical myxomas were associated with a higher risk of embolism, a result rarely reported before. Initially, we thought it may be due to their appearance and tumor location. Unfortunately, however, the prevalence of the 2 types of macroscopic tumors (solid *vs.* papillary) was not significantly different in typical (50.4% *vs.* 49.6%) and atypical locations (59.6 *vs.* 40.4%) (P=0.2470), consistent with previous findings [9]. We speculate that the atypical location plays a greater and more important role than the typical location in hemodynamics. Further investigation is needed to confirm this speculation.

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Table 7. Multivariate analysis of risk factors for myxoma-related embolism.

	Univariable correlates			Multivariable risk factors	
	Parameter estimate (SE)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	–0.0262	0.974 (0.948–1.001)	0.0595		
Sex	0.4056	1.500 (0.679–3.315)	0.3161		
Atrial fibrillation	0.2878	1.333 (0.340–5.229)	0.6798		
Hyperlipidemia	0.8771	2.404 (0.659–8.763)	0.1838		
Valvular heart disease	–0.1612	0.851 (0.337–2.151)	0.7333		
Platelet count (>300×10^9/L)	0.9863	2.681 (1.097–6.555)	0.0306	2.911 (1.074–7.887)	0.0356
Type 1 appearance	0.8563	2.355 (1.068–5.190)	0.0337	2.487 (1.072–5.768)	0.0338
Size (>25 cm^2) (n)	0.4093	2.423 (1.090–5.423)	0.0299		
Typical location	0.9267	2.526 (1.143–5.584)	0.0220	2.533 (1.066–6.022)	0.0354
MPV	0.3836	1.468 (1.062–2.027)	0.0200	1.606 (1.113–2.317)	0.0113

Tumor size in myxomas as a risk factor of embolism was inconsistent in previous studies [7,13,15,23]. Our study found that tumor size did not differ significantly between the embolic and non-embolic groups. However, apparently large myxomas (>25 mm^2) were associated with a higher risk of embolic events in the univariate analysis. The multivariate analysis indicated that large myxoma was a confounding factor. However, it was a factor underlying embolism, since the bigger tumor offered larger interactive area between the myxoma and the coagulation factors. Studies with larger sample sizes are needed to confirm the association.

Irregular surface, atypical location, and higher MPV and platelet count enabled the analysis of embolic risk in patients with cardiac myxoma. Prompt surgical excision of myxomas is indicated for patients at increased risk of embolism. Furthermore, these indices reflect the level of tumor fragmentation. Myxomas with tumor fragments are used to assess the risk of embolization during surgery.

In our study, only 7.4% of the patients showed atrial fibrillation, 6.79% manifested hyperlipidemia, and 5.6% were diagnosed with diabetes. However, these common embolic risk factors do not affect myxoma-related embolism, which is consistent with previous findings [17,23].

Limitations

Owing to the retrospective nature and the long period of data collection, some valuable data were overlooked. For instance, the mobility of myxoma depends on its consistency, the level of attachment, and pedicle length, all of which are related to embolic risks [7,13,15,23]. We found very few cases with pedicle length. The degree of attachment and consistency was not adequate for analysis of myxoma mobility. Our study results are also limited by the different recruitment periods.

Conclusions

The tumor size, location, and macroscopic appearance, along with MPV and platelet count, are closely associated with embolic events in patients with cardiac myxoma. Patients with higher embolic risks should undergo surgical excision promptly, with caution exercised to prevent embolization during the surgery.

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