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Review Article

Clinical characteristics and surgical outcomes of cardiac myxoma: A meta-analysis of worldwide experience

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ABSTRACT

Cardiac myxoma is the most common primary cardiac tumor. However, existing literature mainly consists of single-center experiences with limited subjects. This systematic review aimed to provide data on clinical characteristics and surgical outcomes of cardiac myxoma. We performed a thorough literature search on May 23, 2023 on PubMed, ProQuest, ScienceDirect, Scopus, and Web of Science. The inclusion criteria were English full-text, observational studies, and included >20 subjects. From the search, 112 studies with a total of 8150 patients were included in the analysis. The mean age was 51 years (95 % confidence interval [95%CI] = 49.1–52.3), and the majority were females (64.3 % [95 % CI = 62.8–65.8 %]). The most common clinical manifestation was cardiovascular symptoms. Echocardiography can diagnose almost all cases (98.1 % [95 % CI = 95.8–99.6 %]). Cardiac myxoma was mostly prevalent in left atrium (85.3 % [95%CI = 83.3–87 %]) and predominantly with pedunculated morphology (75.6 % [95%CI = 64.1–84.3 %]). Post-tumor excision outcomes were excellent, with an early mortality of 1.27 % (95 % CI = 0.8–1.8 %), late mortality rate of 4.7 (95 % CI = 2.5–7.4) per 1000 person-years, and recurrence rate at 0.5 (95 % CI = 0.0–1.1) per 1000 person-years. Tumor excision is warranted in a timely manner once the cardiac myxoma diagnosis is established.

1. Introduction

Cardiac myxoma (CM) is the most common cardiac tumor, comprising 50–85 % of all primary cardiac tumors [1] and estimated incidence of 0.03 % in general population [2–8]. Although CM is rarely encountered, however, it can cause serious morbidity and mortality if not treated well in a timely manner. The diagnosis of myxoma may be missed and delayed as it poses various clinical manifestations. In addition, CM can cause sudden death due to intracardiac obstruction and systemic emboli [3].

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Some studies emphasize the roles of echocardiography to diagnose CM and surgical management is warranted once the diagnosis is established. However, the majority of publication about CM is from single-center studies with limited subjects which made the uncertainty of evidence.

On the other side, understanding CM characteristics is important to improve patient management algorithms and outcomes. However, solid evidence is absent. For that reason, we conduct an exhaustive systematic review and meta-analysis to provide a comprehensive characteristic of natural history of CM. This meta-analysis aims to provide the demographic and clinical characteristics, as well as surgical outcomes (early mortality, late mortality, and recurrence) of CM.

2. Method

This systematic review has been registered with PROSPERO (CRD42022344422) and was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 [9] **(Table S1)**.

2.1. Eligibility criteria

All types of clinical studies were included in this review. The inclusion criteria were as follows: (1) full-text English literature, (2) mentioning the prevalence of CM found during the study period, and (3) an observational design. Studies that consisted of fewer than 20 subjects were excluded. If multiple studies were using the same database, only the article with the longest study period was included. Review studies, as well as systematic reviews and meta-analyses, were excluded. Studies focusing exclusively on specific types of CM, such as only left atrial myxoma or Carney-Complex CM, were also excluded.

2.2. Search Strategy and selection of studies

Databases (Science Direct, Scopus, Web of Science, PubMed, and ProQuest) were searched using terms ("cardiac myxoma") OR ("atrial myxoma") OR ("ventricular myxoma")) AND ("clinical presentation"). The search was conducted on May 23, 2023. The results were then deduplicated and screened by three reviewers (PBTS, JNA, and LAY). The screening was conducted by reading the abstract to match the inclusion criteria. Further, the full text of the studies was retrieved to assess their eligibility criteria. References of included studies were screened to collect possible included studies that were not covered by the search method to cover grey literature.

2.3. Data extraction

The extracted variables include the following: study period, center name, country, sex, total number of CM cases, age, diagnosis modality, myxoma characteristics (location, size, number of pedunculated myxomas), main symptoms, surgical characteristics (number of concurrent cardiac procedures, surgical approach, total number of surgeries, tumor excision methods, and minimally invasive procedures), and outcomes (early mortality, late mortality, recurrence, and follow-up duration).

2.4. Quality assessment

Collected studies were analyzed independently by three authors (PBTS, JNA, LAY) using Newcastle-Ottawa Quality Assessment Scale (NOS) for observational studies to assess the quality of evidence in each study [10]. Each item in NOS is valued by "0" (when the item was not contemplated) or "1" (if the item was contemplated); a maximum score of 2 could be given for the item "comparability." The cumulative score from 0 to 9 divides the studies with ratings 0–2 (poor quality), 3–5 (fair quality), and 6–9 (good/high quality). Studies with moderate and high-quality assessments were included.

2.5. Outcome measures

The primary outcome of this meta-analysis was postoperative outcomes, consisting of (1) prevalence of early mortality, (2) incidence rate of late mortality, and (3) incidence rate of recurrence. Early mortality is defined as in-hospital mortality and 30-day mortality. Moreover, secondary outcomes were predefined in the following: (a) demographic characteristics, such as pooled age (mean ± SD) in years and prevalence of females among all CM patients; (b) the utilization of echocardiography as a diagnostic tool to diagnose myxoma and the basis for deciding tumor resection which was estimated as prevalence; and (c) the prevalence of CM location (left atrium, right atrium, left ventricle, right ventricle, and valvular myxoma – defined as myxoma that is attached to heart valve).

2.6. Statistical analysis

The data were summarized and presented by quantitative techniques, employing meta-analysis of single prevalence and incidence rate. The meta-analysis was performed using R software version 4.2.2 (Posit PBC, USA). Pooled prevalence and rate were estimated by applying random effects meta-analysis to anticipate the nature of heterogeneity of included studies. The prevalence was estimated using the inverse of the variance of the logit-transformed proportion as default. However, Freeman-Tukey double arcsine transformation would be preferred when we encountered zero events during analysis. To assess between studies heterogeneity, the I^2 test was chosen, with I^2 values exceeding 50 % indicating moderate-to-high heterogeneity. Subgroup analyses were conducted to explore potential sources of heterogeneity of primary outcomes, focusing on variables such as type of study location (single- or multicenter), annual caseload, continents, and follow-up duration. Sensitivity analyses were performed to evaluate the influence of individual studies on the overall result. Leave-one-out sensitivity analysis and/or exclusion of potential outlier studies (as indicated by Baujat Plot) were employed for this purpose. Publication bias was examined visually using Funnel's plot and statistically through Egger's regression test. If significant publication bias was detected, the Duval and Tweedie trim and fill methods were applied to generate adjusted effect estimates. Statistical significance was set at a p-value less than 0.05 for all analyses.

3. Results

3.1. Study selection and quality assessment

A total of 4414 studies were identified after primary search in five large databases, of which 147 studies were removed during the detection of duplications. A number of 4067 studies were excluded during the title and abstract screening, while 85 studies were not eligible after a full-text review (Fig. 1). Citation searching to cover grey literature contributed to an additional 7 included studies. We excluded some studies due to the lack of study subject ($N < 20$) [11–22], wrong studies [20,23–28], English full text was not available [29–31], articles from overlaps studies [32–42], outcome of interest were not available [43–46] and others. Finally, 112 studies [4–8,35,47–152] were included in this systematic review and meta-analysis. Eligible studies were subsequently assessed for quality assessment, as detailed in Table S2. All included studies were considered good/high quality, with NOS score ≥6 **(Table S2)**.

3.2. Study characteristics

A total of 8150 patients from 112 observational studies were included in this review. All the included studies were retrospective, except for one prospective study conducted by Bossert et al. [66]. The publication years of included studies were between 1986 and 2022, and

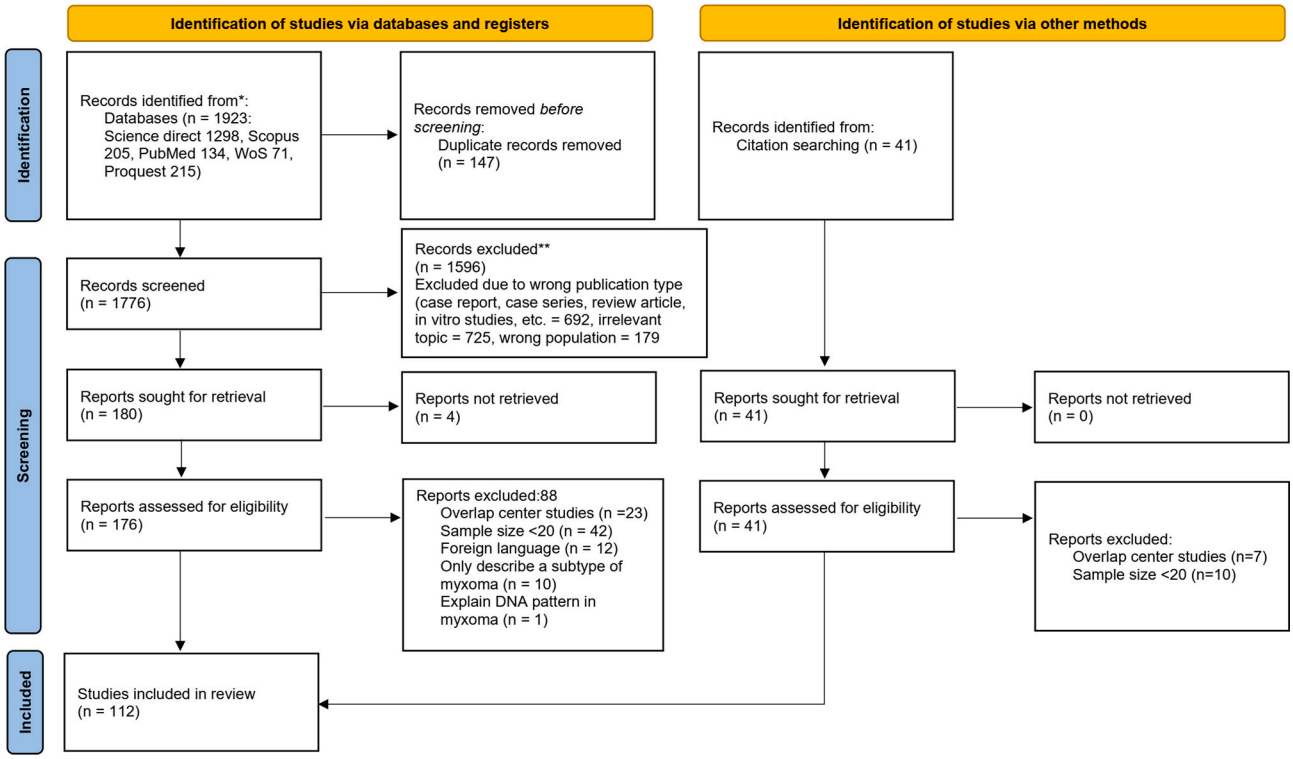

Fig. 1. Prisma Flowchart of study selection process.

more than three-quarters of studies were published after 2000. The majority of published articles (83.0 %) were from single-center experiences. Most studies are conducted in Asia (45,5 %) and Europe (39.3 %), followed by 12.5 % studies from North America continents. There were only two studies from South America and one study from Africa. Out of 40 reporting countries, China becomes the country with the largest output, contributing to 12.5 % of included studies, followed by the USA (11.6 %), Italy (10.7 %), India (8.9 %), and Turkey (8.9 %). The mean study period was 16.5 ± 8.2 years. The median patient number and annual caseload for the single-center study were 50 patients (IQR, 30–73.5) and 3.2 cases/years (IQR 1.8–6.1), respectively (Table S3).

From 91 studies concerning presenting symptoms, the majority of CM patients complained of dyspnea as the main symptom in 64 of 91 studies. The other frequently reported cardiovascular or hemodynamic symptoms were palpitation, heart failure, and syncope. A total of 54 studies reported the thoracotomy approach, in which median sternotomy was the most common surgical approach for tumor resection in all studies. Moreover, the minimally invasive technique was noticed and reported in studies published after 2000 [64,66,98,104,145]. By aggregating 18 studies reporting aortic cross-clamp duration, with a total of 1039 cases, the pooled mean of this procedure was 46.7 min (95 % CI 41.40–53.08, $I^2 = 96.1$ %) (Fig. S1). In a similar way, we noted the pooled mean of the cardiopulmonary bypass process was 76.2 min (95% CI 70.06–82.38, $I^2 = 92$ %), generated from 19 reporting studies with a total of 1143 patients (Fig. S1).

3.3. Primary outcomes

3.3.1. Post-surgical early mortality prevalence

A total of 86 studies comprising 5184 patients reported on the prevalence of early mortality among CM patients following tumor resection. Of these studies, 36 (41.9 %) reported zero cases of early mortality. Our pooled analysis revealed that the prevalence of early mortality was 1 % (Fig. 2), which also possessed negligible heterogeneity ($I^2 = 24$ %). The funnel plot (Fig. S2) also exhibited visual symmetry, which was further confirmed by Egger's regression test ($p > 0.05$), indicating of nonsignificant publication bias influence. Additionally, we also provided a geospatial data visualization to depict the prevalence of early mortality in each reporting country in Fig. 3 (primary data from Fig. S3).

3.3.2. Post-surgical late mortality rate

In our analysis, a total of 53 studies were included, which provided data on both the number of late mortalities and the median follow-up periods was 6 (IQR = 4–8) years. This allowed us to calculate the late mortality rate in patients with CM undergoing tumor resection surgery. Our pooled analysis revealed that the rate of late mortality was 4 death per 1000 person-years (late mortality rate 4.70 [2.49–7.40], $I^2 = 70.0$ %) (Fig. 4). Moreover, we observed a noteworthy presence of publication bias, as evidenced by funnel plot asymmetry (Fig. S8), and this was further confirmed by a significant Egger's regression test result ($p < 0.001$). To account for this bias and obtain a more accurate estimate, we performed a trim-and-fill analysis, which generated a new adjusted estimate of 2 cases per 1000 person-years (adjusted late mortality rate 2.0 [0.2–5.0]), with an I^2 value of 77.8 %.

As we noted a significant heterogeneity, subgroup analyses were then performed based on several variables, including the type of study center (single- or multi-center), center annual caseload (measured as cases per year), geographical continents, and follow-up periods. However, our analysis further did not reveal a significant reduction in heterogeneity within each subgroup (Fig. S4). Notably, the continents subgroup showed significant differences in mortality rate among major continents, which was highest in North American countries, followed by European countries. We then proceeded to perform the leave-one-out sensitivity analysis though there was no marked reduction in observed heterogeneity. Nevertheless, Baujat's plot analysis further identified ten potential studies [5,49,72,82,89,93,119,124,144,153] which considerably contributed to the observed heterogeneity (Fig. S5). Excluding those ten studies results in a significant reduction of heterogeneity and the pooled mortality rate. We continued performing sensitivity analysis by excluding the top seven and then five influencing studies [49,72,89,93,144], resulting in significant pooled estimate improvement with

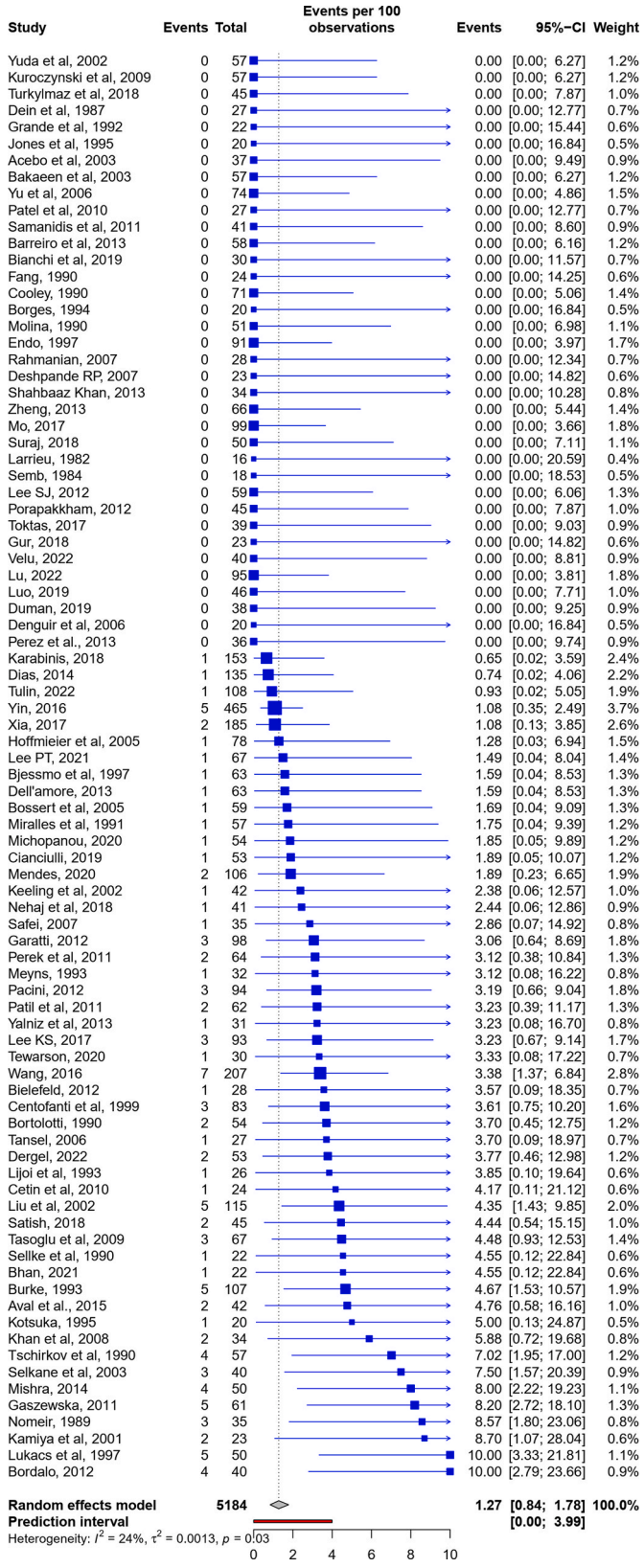

Fig. 2. Prevalence of early mortality in cardiac myxoma patients.

acceptable heterogeneity, which was 3.9 and 4.9 per 1000 person-years. In Fig. S6, we have additionally presented the geospatial data visualization of countries that reported the late mortality rate in patients undergoing CM tumor resection surgery, which was revealing the higher rate in some European countries, Japan, and the USA.

3.3.3. Post-surgical recurrence rate

From 60 studies reporting on the myxoma recurrences (median of follow-up periods 6 [IQR = 4–8] years), pooled statistical analysis showed the recurrence rate of CM following surgery was 0.5 cases per 1000 person-years (recurrence rate 0.47 [95%CI 0.07–1.13], $I^2 = 24$ %] (Fig. 5). Further publication bias analysis indicated the presence of this bias (Fig. S9) and was statistically evidenced by Egger's test ($p < 0.001$). The Duval and Tweedie's trim and fill analysis was then employed to generate a new adjusted estimate, which was 0.03 cases per 1000 person-years (adjusted recurrence rate 0.03 [95%CI 0.0–0.4], $I^2 = 37.5$ %]).

3.4. Secondary outcomes

3.4.1. Demographic characteristics of patients with cardiac myxoma

In a meta-analysis of 96 studies, encompassing a total of 7313 cases, it was found that CM exhibited a higher occurrence among females, accounting for 64 % of the cases (Fig. S10). The analysis demonstrated a noteworthy consistency in this trend across the amalgamated data, with acceptable heterogeneity observed ($I^2 = 31$ %). The funnel plot showed symmetric, further confirmed by insignificant Egger's test result ($p > 0.05$), suggesting the low probability of publication bias presence (Fig. S11A). Moreover, our summary of 88 studies with a cumulative of 6872 patients yielded the mean of patients diagnosed with CM was 51 years, with evidence of significant heterogeneity ($I^2 = 98$ %) (Fig. S10B). This might be rooted in the dispersed range of reported ages in each study, which lay from 9 to 67 years, ranging from pediatric to geriatric patients. Publication bias analyses were conducted and failed to demonstrate the significant influence of this bias in this analysis (Egger's Test $p > 0.05$) (Fig. S11B).

3.4.2. Prevalence of echocardiography as the diagnostic modality for cardiac myxoma

A total of 69 studies were included in the analysis to assess the diagnostic modalities used for CM detection. As illustrated in Fig. S12, echocardiography emerged as the predominant diagnostic modality, being utilized in most cases (98.1 %). Additionally, a smaller proportion of cases were diagnosed through computed tomography scans, angiography, magnetic resonance imaging, and intraoperative approaches. It is important to note that the analysis revealed a substantial degree of heterogeneity ($I^2 = 92$ %, $p < 0.01$). However, upon the exclusion of potential outliers [41,58,62,78,123] (Fig. S13), a significant reduction in heterogeneity was observed ($I^2 = 53$ %). This exclusion allowed for the calculation of a pooled estimate indicating a near-universal utilization of echocardiography (99.7 % [95 % CI 99.2 %–100.0 %]) for diagnosing CM. Furthermore, the assessment of publication bias indicated discernible influence, as indicated by Begg funnel plot asymmetry, despite insignificant Egger's test results ($p = 0.07$) (Fig. S14). To address this potential bias, trim and fill analysis was performed, yielding a similar adjusted prevalence estimate for echocardiography utilization at 99.7 % (95 % CI 99.2–100.0, $I^2 = 53.8$ %) as there were no applicable filling methods.

3.4.3. Prevalence of cardiac myxoma according to its location and morphology

The finding from 107 studies and 7156 patients allowed us to examine the distribution of myxoma locations in the heart. Our analysis revealed that the left atrium was the most common site, accounting for 85 % of the cases, followed by the right atrium (9 %), with the remaining cases arising from various other locations (Fig. 6). Notably, the analysis of the left and right atrium locations exhibited significant heterogeneity (Fig. 6). We performed sensitivity analysis by finding and excluding the potential outliers depicted by their respective Baujat Plot. After excluding two outliers [79,104]. (Fig. S15), there was a significant

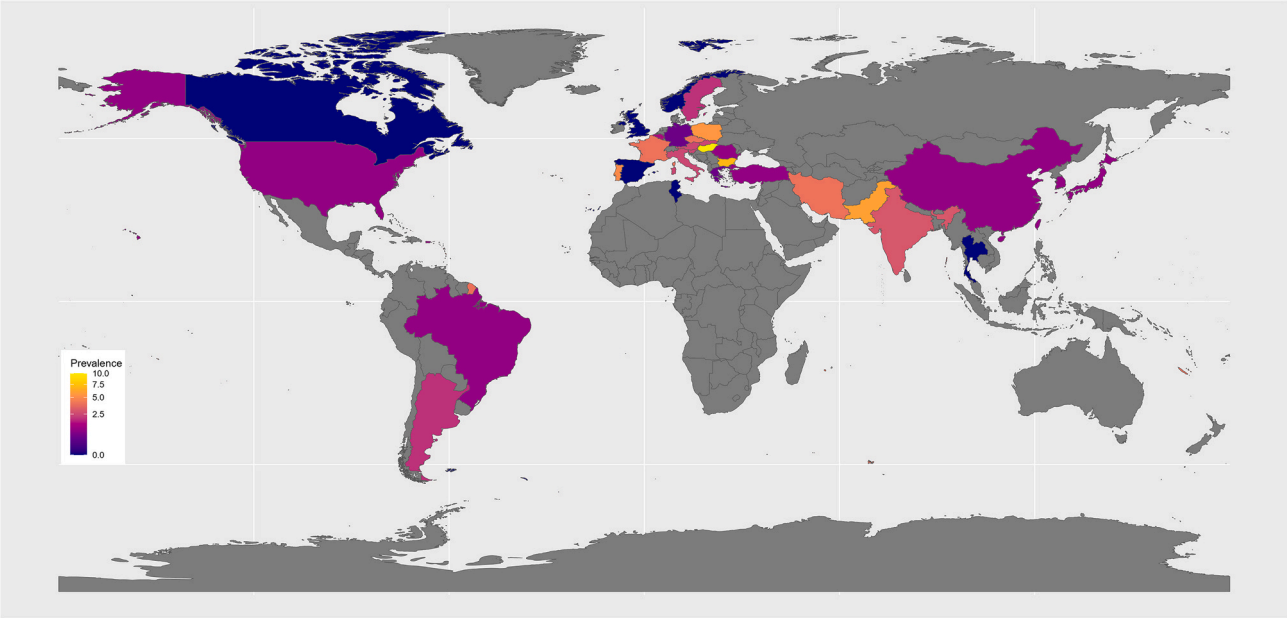

Fig. 3. Geospatial visualization of Global prevalence of early mortality.

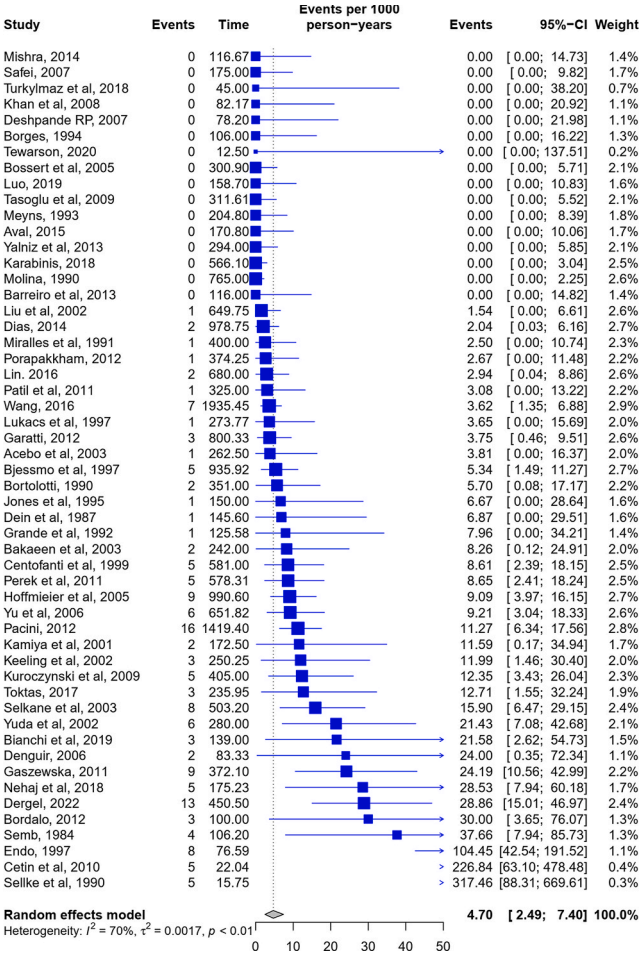

Fig. 4. Forest plot of late mortality rate.

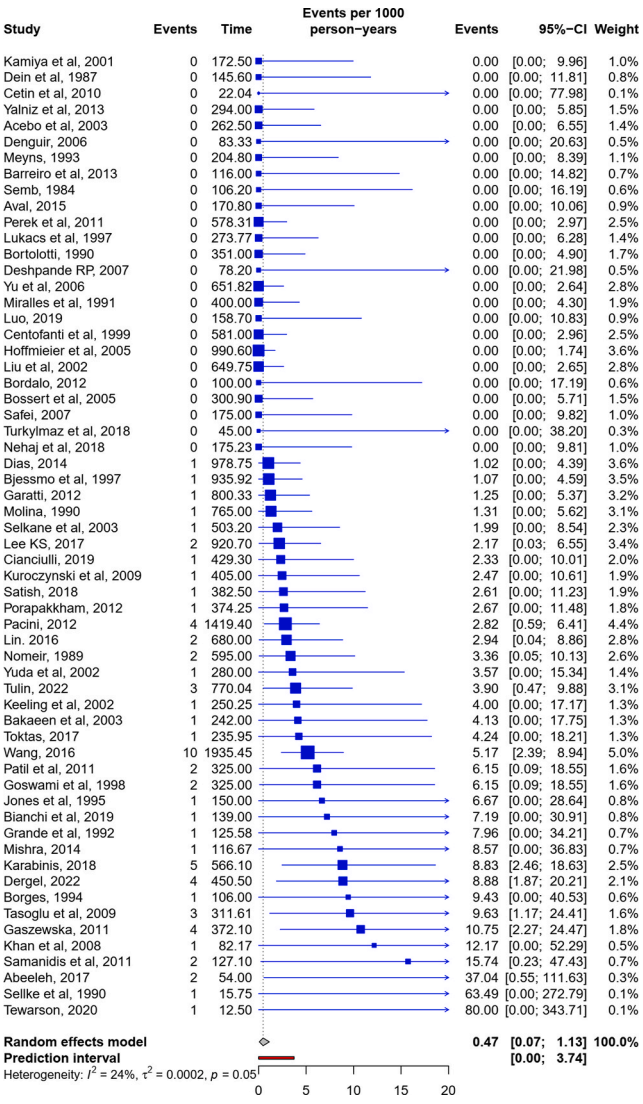

Fig. 5. Forest plot of cardiac myxoma recurrence rate after surgery.

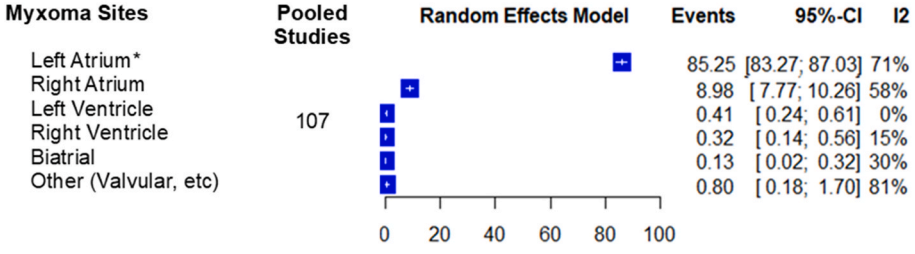

Fig. 6. Cardiac myxoma location distribution.

reduction of heterogeneity without significant change of pooled estimate of left atrium location, which was 85.76 % (95%CI 84.25–87.15, I^2 = 54.9 %). Similarly, for the right atrium location, there was a marked reduction of heterogeneity (I^2 = 36.4 %) after excluding one study by Yalniz et al., 2013 [79] (Fig. S15). Publication bias analyses on both outcomes did not find a significant publication bias influence (Fig. S16). Furthermore, the majority of CM cases were observed to be pedunculated, accounting for 76 % of all instances (Fig. S17). Nevertheless, this outcome also exhibited significant heterogeneity, as indicated by I^2 = 86 %. After excluding two outliers, the heterogeneity was only slightly reduced to I^2 = 56 %, while maintaining the pooled estimate at 77 %. Moreover, a publication bias analysis was conducted, and it did not identify any significant influence of publication bias (Egger's regression test $p > 0.05$) (Fig. S18).

4. Discussion

A total of 112 studies, comprising 8150 CM patients with 36 study years, were pooled in this meta-analysis. To the best of our knowledge, this is the first systematic review and meta-analysis specifically

examining the characteristics of CM. Cardiac myxoma is more prevalent in females (64 %). In comparison, valvular CM [24,154] and familial CM [46] were more prevalent in male. However, our meta-analysis revealed valvular myxoma comprises of <1 % of total CM cases. Additionally, CM is commonly diagnosed within four to six decades of life, especially around the age of 50. In contrast, familial and complex CM have an earlier onset compared to common CM, which is typically diagnosed between the ages of 20 and 30 years old [46]. Familial and complex CM were excluded from this systematic review because they were considered distinct entities from common sporadic CM [15,24,44,46]

The most frequent presenting symptom of CM patients was dyspnea in 70 % of studies, followed by cardiovascular or hemodynamic symptoms such as palpitation, heart failure, and syncope. CM symptoms depend on the tumor size, location, mobility, invasiveness, and friability [63]. Cardiovascular symptoms can result from the obstruction of an outflow tract or significant regurgitation due to the tumor. In some cases, especially valvular myxoma, the mass detaches and impairs valvular function and structure [154]. The majority of CM was pedunculated (76 %). The peduncle structure makes the tumor freely move during cardiac cycle that can cause sudden death due to total obstruction or tumor dislodgment. In addition, this pedunculated characteristic can also be used as a clue to differentiate CM from other sessile structures such as cardiac malignancy and thrombus.

Embolic symptoms became one of the frequently reported symptoms after cardiac symptoms. Long-term obstruction or regurgitation promotes pressure and/or volume overload, further inducing chamber enlargement and wall remodeling. An analysis of 7156 patients revealed that 85 % of CM cases are prevalent in left atrium followed by 9 % in right atrium. Left atrial enlargement and wall remodeling can causes atrial fibrillation that promote thrombus formation. [155]In addition, the rupture of a tumor, even in a small fragment size, potentially promotes coagulation cascade activation that results in lethal embolus. That may explain why embolic symptoms in CM are more commonly manifested as systemic embolus (e.g. stroke and acute limb ischemia) than pulmonary embolus [155–157]. There is also a small number of patients that have myxoma in both atrium or ventricular chambers. Sudden death due to a tumor or thrombus emboly may occur if an emergency myxoma case is not excised in a timely manner.

Tumor excision is paramount in CM management; however, it requires an established diagnosis. Our meta-analysis revealed that echocardiography can diagnose up to 98 % of CM cases. Thus, we recommend echocardiography as the only required modality to diagnose CM. Echocardiography is also an affordable, non-invasive, and simple examination [100,158]. It can delineate cardiac tumor size, morphology, extension, attachment, pedunculated characteristic as well as its hemodynamic manifestation. In a small number of inconclusive cases, second-line diagnostic modalities such as magnetic resonance or enhanced CT scan may be used to confirm the diagnosis or exclude differential diagnoses [159]. As a note, we found 12 intraoperatively diagnosed cases due to various reasons, including the failure of diagnostic modalities to confirm CM diagnosis [48,49,52,62,72,82,87]. However, all cases except for two cases [72,82] were reported before the year 2000, which is considered the era when echocardiography scarcely used as a diagnostic modality. Included, studies showed that angiography was one of the most common diagnostic modalities to establish CM diagnosis before the year 2000 when echocardiography was not yet familiarly used worldwide.

Tumor excision should be promptly performed after the diagnosis to prevent sudden death, especially in patients with hemodynamic instability (e.g., syncope or congestive heart failure) [154]. A watchful waiting approach for CM potentially leads to sudden death due to complete obstruction, dislodged mass, or a lethal embolus. Median sternotomy remains the most common surgical approach for myxoma excision. However, the minimally invasive approach appears to be emerging, especially in developed countries [34,64,66,104,145]. We found that the mean aortic cross-clamp time for CM excision is 46.74 min, and the mean cardiopulmonary bypass time is 76.22 min. The outcomes of surgery vary based on each center's experience. The prevalence of early mortality (defined as in-hospital mortality and 30-day mortality) after surgery is 1 %. Additionally, the incidence of late mortality following myxoma excision is 5 cases per 1000 patient-years (2 cases per 1000 patient-years after publication bias adjustment). Both early and late mortality rates for CM following surgery were considerably excellent. This result was affected by neither the continents, follow-up duration, or center annual center load after subgroup analysis (Fig. S5). This result is consistent with previous studies showing excellent short- and long-term mortality for benign cardiac tumor resection [160]. More than 80 % of patients remain without cardiovascular manifestation after myxoma resection [58]. Tissue repair or replacement may only be needed in a limited number of cases. However, it is worth noting that delaying tumor resection results in a threefold increase in mortality compared to early resection [58,154]. Thus, an excellent prognosis for myxoma can be achieved when the tumor is resected in a timely manner.

Another important outcome indicator for tumor resection is recurrence, which has a low value of 0.5 cases per 1000 person-years. Although not specific to myxoma, a previous meta-analysis also showed that the recurrence rate of benign cardiac tumors is low [160]. Recurrence may result from inadequate tumor resection, especially for tumors located in vital areas or deeply invasive masses [154]. It may also be caused by cytotransplantation or systemic embolization [12], which may be prevented by firm embolization blockade (e.g., gauze), especially for tumors located near ventricular outflow track [154]. Overall, although CM can cause substantial symptoms and sudden death, CM outcomes following surgery are excellent in the aspects of early mortality, late mortality, and recurrence.

We acknowledge several limitations in our study. First, the data source primarily relied on retrospective observational studies conducted at a single center, each with its methodological limitations and inherent selection biases. We had attempted to address this limitation by setting a minimum requirement of 20 CM subjects for inclusion in our study. Second, in order to address the disparate reporting of age data among the studies, we implemented a transformation to mean ± SD. Third, certain parameters such as histopathology, tumor invasiveness, and the extent of resection could not be obtained from each included study as they were not reported.

In conclusion, CM is more commonly found in females, particularly in those aged between forty to sixty years, with dyspnea emerging as the predominant and frequent presenting symptom. Echocardiography is recommended as a non-invasive diagnostic tool that can diagnose almost all cases of CM. The majority of CMs are pedunculated and located in the left atrium. Excision of myxomas is associated with an excellent prognosis in terms of short- and long-term mortality, as well as a low recurrence rate. Prompt surgical intervention is required after the CM diagnosis is established.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author contributions statement

Study concepts: P.B.T. Saputra, Y.H.Oktaviono. **Study design**: P.B.T. Saputra, Y.H. Oktaviono, J.N. Arnindita, L.S. Afgriyuspita. **Data acquisition**: L.S. Afgriyuspita, J.N. Arnindita, P.B.T. Saputra, D. Pasahari. **Quality control of data and algorithms**: Y.H. Oktaviono, C.D.K. Wungu, H. Susilo, F.F. Alkaff. **Data analysis and interpretation**: P.B.T Saputra, R.B. Kurniawan, C. Milla. **Statistical analysis**: R.B. Kurniawan, C. Milla. **Manuscript preparation**: P.B.T. Saputra, Y.H. Oktaviono, J.N. Arnindita, L.S. Afgriyuspita, R.B. Kurniawan, D. Pasahari, C. Milla. **Manuscript editing:** P.B.T. Saputra, Y.H. Oktaviono, J.N. Arnindita, L.

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Declaration of competing interest

None.

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List of abbreviation

CM	Cardiac myxoma
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
NOS	Newcastle-Ottawa Quality Assessment Scale
SD	Standard deviation
USA	United States of America
IQR	Interquartile range

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.107940.

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