Minimally invasive approaches to primary cardiac tumors: a systematic review and meta-analysis.

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Abstract

Objective: Cardiac tumors are rare conditions. The vast majority of them are benign yet they may lead to serious complications. Complete surgical resection is the gold standard treatment and should be performed as soon as the diagnosis is made. Median sternotomy (MS) is the standard approach and provides excellent early outcomes and durable results at follow-up. However, minimally invasive (MI) is gaining popularity and its role in the treatment of cardiac tumors needs further clarification. Methods: A systematic literature review identified 12 candidate studies; of these, 11 met the meta-analysis criteria. We analyzed outcomes of 653 subjects (294 MI and 359 MS) with random effects modeling. Each study was assessed for heterogeneity. The primary endpoints were mortality at follow-up and tumor relapse. Secondary endpoints included relevant intra- and post-operative outcomes; tumor size was also considered. Results: There were no significant between-group differences in terms of late mortality (incidence rate ratio (IRR): MI vs. MS, 0.98 [95% CI: 0.25¬–3.82], p = 0.98). Few relapses and redo surgery were observed in both groups (IRR: 1.13[0.26-4.88], p=0.87);(IRR: 1.92 [95% CI: 0.39-9.53], p=0.42); MI was associated to prolonged operation time yet with no effects on clinical outcomes. Tumor size did not significantly differ between groups. Conclusions: Both MI and MS are associated with excellent early and late outcomes with acceptable survival rate and low incidence of recurrences. This study confirms that cardiac tumor may be approached safely and radically with a MI approach.

Introduction

Primary cardiac tumors are rare entities[1]. Approximately 75% are benign with nearly 50% being myxoma[2, 3]. Surgery should be performed soon after diagnosis. The long-term prognosis of benign tumors is excellent[1], but complete removal of the mass is mandatory. Cardiac tumors should be excised with a margin of normal tissue in order to reduce the potential for recurrence. While recurrence rates of benign cardiac tumors are low, relapse is likely the consequence of inadequate excision of the tumor[4]. Additionally, cardiac chambers should be irrigated and suctioned to prevent embolization of fragments. If a defect is created, it should be closed primarily or with a patch. Median sternotomy (MS) is the common approach for cardiac tumor since it provides excellent exposure. This traditional approach is associated with excellent early and late clinical outcomes and remains the gold standard treatment for primary cardiac tumors[1].

Minimally invasive (MI) surgery has emerged as an alternative method to MS. Nevertheless, a main criticism of the MI approach is that, given the limited exposure of the surgical field and the surrounding structures, complete and durable eradication of the cardiac tumor may be compromised compared to the MS approach.

Therefore, the aim of this pairwise meta-analysis was to investigate whether MI may achieve the same early and late outcomes as MS surgery in the context of primary cardiac masses.

Methods

Search strategy

Ethical and internal review board approval was not required for this analysis as no human or animal subjects were involved and no individual patient data was used*;* need for patients' consent was waived. Data will be available on request.

The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[5] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines[6]. We performed a search of the PubMed, Google Scholar, Ovid MEDLINE, and Ovid EMBASE databases for studies on minimal access surgery. Searches were performed during September of 2019 and used the following search terms: (a) 'minimally invasive cardiac tumor' [Title/Abstract]; (b) 'cardiac tumor' [Title/Abstract]; (c) 'cardiac myxomas' [Title/Abstract]; (d) 'benign cardiac tumor' [Title/Abstract]; (e) 'primary cardiac tumor' [Title/Abstract]; and (f) 'valve tumors'[Title/Abstract].

Study selection and inclusion criteria

Articles reporting early and late outcomes for MI and MS procedures were included. Studies were excluded from the analysis if: data was in a non-extractable format; data was duplicated; or the research was performed in an animal model. Two assessors (M.M., M.R.) independently reviewed the titles and abstracts of potentially eligible studies and selected studies that met the inclusion/exclusion criteria for full-text retrieval and further examination. Any disagreement was resolved by discussion with a third author (M.G.). Inter-rater agreement was assessed using Cohen's $\varkappa$ coefficient.

Outcomes

The primary outcome was late mortality and tumor relapse at last follow-up. Secondary outcomes were: cardiopulmonary bypass (CPB) and cross clamp (CC) times, tumor size, re-exploration for bleeding, renal failure, respiratory failure, neurological complications (transient ischemic attack and stroke), in-hospital mortality, re-do surgery at follow-up and total length of stay (LoS). Need for conversion to sternotomy was also recorded in the MI group as a safety endpoint.

Quality scoring

Modified Newcastle–Ottawa scale was used for quality assessment of each study. Studies attaining equal/greater than the median score of 10 (out of a maximum 19) were defined to have 'higher matching quality'[6]. Modified Newcastle–Ottawa scoring criteria are shown in table 1 and quality scoring results are reported in supplementary table 1.

Heterogeneity and publication bias

Inter-study heterogeneity was explored using the Chi^2-statistic, but the I2 value was calculated to quantify the degree of heterogeneity across trials that could not be attributable to chance alone. If heterogeneity was significant ($I^2 > 75\%$), 3 strategies were used to assess data validity and heterogeneity: (1) a subgroup analysis of higher quality studies (quality score [?]10); (2) funnel plots to evaluate publication bias (i.e., funnel asymmetry) with Egger's test; and (3) a meta-regression to assess the effects of covariates on the primary outcome of interest.

A domain-based evaluation of risk of bias was performed in accordance with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.08 as previously described[7]. Three authors (MM, MG, GN) subjectively reviewed all studies included in this review and assigned a value of 'critical', 'serious', 'moderate' or 'low' to the following questions: (Domain 1) Was the allocation sequence adequately generated? (D2) Was allocation adequately concealed? (D3) Was the treatment adequately classified? (D4) Were data affected by deviation from intended intervention? (D5) Were incomplete outcome

data sufficiently assessed? (D6) Are reports in the study free of the suggestion of selecting outcome measures or (D7) of selective outcome reporting?; 'Risk of bias' plots were performed using package 'plotvis' R-project, following the Review Manager® Version 5.3 layout (The Cochrane Collaboration, Software Update, Oxford, UK).

Statistical analysis

Measurement data are reported as the mean ± standard deviation. The analysis used a random effects model (inverse-variance method). For short term categorical outcomes, risk difference with 95% confidence interval were used, as many studies have zero events in both sides. For continuous outcomes, standardized mean difference (SMD) and 95%CI were used. For late outcomes, incidence rate ratio and 95%CI were estimated from the total number of events observed within a treatment group out of the total person-time of follow-up for that treatment group[8]. Meta-regression was used to assess the effect of sample size, age, gender, chronic obstructive pulmonary disease, New York Heart Association (NYHA), previous stroke/transient ischemic attack (TIA) and redo surgery on the primary outcomes and secondary outcome (perioperative mortality).

Hypothesis testing for equivalence was set at the 2-tailed 0.05 level. Analyses and data modeling were performed with R-project (version 3.3.3 R project for Statistical Computing), following packages were used: 'metafor', 'stats', and 'graphics' for data visualization.

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Results

Study characteristics

Our research revealed 11 studies fulfilling these inclusion criteria[9-19], producing a pooled data set of 653 patients of whom 294 underwent MI and 359 underwent MS cardiac tumor excision (table 3) (figure 1). There was 100% concordance between reviewers equating to a Cohen's kappa coefficient of $\varkappa = 1$. The mean sample size was 59.3 patients (range, 5–250 patients) and the mean follow-up duration was 33.3 months (range, 3.7–56 months). All included studies were retrospective; six studies[10-14, 16] included two homogeneous populations and were considered high-quality (median equal or above 10, Table 2); 601 cardiac masses were myxomas (92%) with most prevalent location at the level of the left atrium (table 2).

Definition of minimally invasive

Studies who were eligible for inclusion in the MI group included those reporting: minimally invasive approach as right mini-thoracotomy (4-6 cm) at the level of the 3rd or 4thintercostal space with or without video assistance, with central and or peripheral cannulation, with external or internal aortic clamping; minimally invasive approach as upper or J-shape mini sternotomy; robotic minimally invasive series.

Given that atrial myxoma was the most frequent cardiac mass, right mini-thoracotomy was the most utilized minimally invasive access[10, 11, 14, 15, 17-19]; for aortic valve masses a parasternal incision (4 to 5 cm with rib resection and reattachment) was performed in some cases[11]. Robotic or robotic assisted approach was used in Shilling[12], Yang[13], Moss[16].

Primary outcome

Results for primary and secondary endpoints in each study are summarized in table 3. There was no difference in mortality at follow-up between patients who underwent MI and MS (IRR: 0.98 [95% CI: 0.25–3.82], p = 0.98) and the groups were homogeneous (χ^2 1.5, I^2 0%, p=0.91). Similarly there was no difference in tumor recurrence (IRR: 1.13[0.26-4.88], p=0.87) with low heterogeneity (p=0.9) (figure 2 A/B). The overall mean follow-up duration was 33.31 months (range 3.7 -56 months).

Secondary end-points

Cardiopulmonary bypass time and cross clamp time were significantly longer in the MI group (SMD 0.73, 95% CI 0.32,1.13, p<.01); (0.32, 95% CI 0.08, 0.56, p<0.1) (Table 3), yet with no effect on post-operative

clinical outcome. On the contrary the MI approach resulted in reduced LoS (SMD -1.59, 95% CI -2.35, -0.82, p<.01); however significant heterogeneity was observed (p<.01). There was no difference in term of reopening for bleeding (RD -0.01, 95% CI -0.03, 0.01, p=0.59), TIA/stroke (RD -0.01, 95% CI -0.03, 0.01, p=0.22), respiratory failure (RD -0.00, 95% CI -0.02, 0.01, p=0.6) and renal failure (-0.00, 95% CI -0.02, 0.01, p=0.62), with no heterogeneity. Need for future re-do surgery was similar among the two groups;(IRR: 1.92 [95% CI: 0.39-9.53], p=0.42), with low-heterogeneity (p=0.98 and 1 respectively).

Tumor size did not differ significantly between MI and MS (SMD -0.47, 95% CI -1.29, 0.35, p=0.26); average maximum diameter was 12.6 vs 13.6 mm for MI and MS respectively.

There was no in-hospital or 30-day mortality. No conversions to sternotomy were reported (table 3).

High-quality studies

The overall quality of studies is summarized in supplementary table 1. Of 11 included studies, 6 were rated as high-quality ([?] 10 points). Subgroup analysis of the high-quality studies revealed no significant between-group difference in terms of the primary outcomes late mortality and recurrence (IRR: 0.47 [95% CI: 0.07–3.07], p = 0.43; IRR: 1.47 [95% CI: 0.09-25.5], p=0.78, respectively) (supplementary figure 1,2); CPB and CC time were significantly longer in the MI group yet no effect on post-operative outcome was noted (supplementary table 2).

Subgroup analysis: robotic

Three studies included robotic surgery. Similar to the overall population, the robotic approach was as safe as the MS approach with similar early post-operative outcomes (supplementary table 3); LOS was significantly reduced in the robotic group (SMD -0.91, 95% CI -1.58, -0.24, p<.01), yet heterogeneity was detected (p<0.01); given the limited robotic sample size, no analysis at follow-up could be carried out.

Heterogeneity assessment: bias exploration

A risk of bias analysis was performed for all included studies as per the Cochrane guidelines . Overall, there was a high level of bias due to the fact that a majority of studies were not randomized or blinded. Moreover, we assigned scores for each of the domains D1-D7. No study fulfilled all of these criteria (figure 3). Funnel plots were used to assess publication bias for all primary and secondary outcomes. There was no funnel plot asymmetry for the primary outcome late survival (supplementary figure 3) and tumor relapse at follow-up (supplementary figure 4).

Meta-regression

In the multi-variable model (total sample size, age, sex, COPD, NYHA class, previous stroke/TIA, redo, CPB), no association with the primary outcome late survival / recurrence or perioperative mortality was observed. Supplementary table 4 provides a list of overall meta-regression coefficients.

Discussion

Minimally invasive cardiac surgery has been reported since the 1990's[14]. Described benefits includes: reduced blood loss and pain, shorter LoS, and generally, superior patient satisfaction[20]. MI was also found beneficial in high-risk patients to reduce surgical trauma[7].

Due to the rarity of intra cardiac masses few studies comparing the outcomes of MI and MS surgery have been published. The present meta-analysis, by aggregating data from 11 studies, confirms that the MI approach for cardiac tumor resection is as safe as MS, with excellent early and late outcomes, very low recurrence rates, and rare need for reoperation at follow-up.

Among the total number of 653 tumors described, 601 (92%) were myxomas, 22 (3.3%) papillary fibroelastoma, 13 (1.9%) thrombus, 6 (0.9%) vascular malformation, 2 (0.3%) lipoma, 1 (0.1%) fibroma, 1 (0.1%) rhabdomyoma, 1 (0.1%) chondrosarcoma, 1 (0.1%) hamartoma, and 5 (0.7%) classified as 'other'. Only Ravikumar[9]included a case of secondary atrial chondrosarcoma.

This study confirms that the MI approach requires prolonged operative time due to longer CPB and CC time. However, there was no demonstrable effect on clinical outcomes and MI had similar rates of post-operative complications as the MS approach. In line with previous studies, LOS was significantly shorter in the MI group[20]. The same results were observed in the subgroup analysis of the high-quality studies[10-14, 16].

Notably, we did not find significant differences in terms of tumor size between groups. We may speculate that large masses may preclude the MI approach. Nevertheless, even in cases of large size of the tumor, the MI approach may be still feasible[21].

Regarding the incidence of recurrences, our results are in line with previously published literature. A retrospective study from the Mayo Clinic spanning over 50 years reported a recurrence rate of 5.6% with a MS approach[22]. Similarly, Keeling et al reported a rate of 2%[23] and in a prospective single cohort series of patients treated with a minimally invasive approach, Bianchi et al[24] reported an incidence of recurrence of 3.3%.

With cardiac myxoma, while a stalk base resection is generally indicated to avoid tumor recurrence, its superiority over endocardial resection is under debate. The Mayo Clinic[22] study demonstrated that there were no differences in tumor recurrence based in resection margin. Nevertheless, we could not analyze the impact of different surgical techniques (e.g. resection with patch, endocardial resection, single vs double atrial approach) on late recurrences.

In our meta-analysis, there were no conversions to sternotomy and the rate of reopening for bleeding was similar between the two groups (safety end-point). The presence of a right atrial tumor has been reported as possible contraindication for a minimally invasive approach due to fragmentation during cannulation procedures[25]. Importantly, there was no difference in the occurrence of post-operative neurological events and no clinically relevant embolization events were observed in the MI group.

All series included in the analysis were low-medium volume, likely due to the rarity of cardiac tumors. With this in mind, we could not evaluate the effect of the surgical cumulative volume on clinical outcomes[4].

While a majority of patients included in this study had benign cardiac tumors, it worth noting that the use of MI has been described in literature in the context of primary malignant tumors[26]. The MI approach has largely been utilized with benign tumors rather than malignant tumors probably due to the greater ease of resection, the less invasive nature of benign tumors, and the lack of need for very complex cardiac reconstructions, which would be difficult with MI access.

Sensitivity analysis of the robotic studies was undermined by the limited sample size; no analysis in terms of survival and relapse at follow-up could be carried out; while we may conclude that the robotic approach may be as safe as MS, we cannot validate the long-term results.

A main limitation inherent to the study design stems from the use of retrospective cohort studies in our pooled analyses. There was a certain degree of clinical heterogeneity; while most of the studies included exclusively myxoma at the level of the left or right atrium, others have included masses at the level of the aortic valve or ventricles. Follow-up times in this analysis were short with respect to tumor recurrence/survival and long-term follow-up was not always available. Finally, no cost-analysis could be performed.

Conclusion

To our knowledge, the present study is the first pairwise meta-analysis comparing the early and late performance of minimally invasive versus sternotomy approaches in the context of cardiac tumors. Minimally invasive surgery was associated with excellent early and late outcomes, comparable to the MS approach. Our analysis showed that the risk of primary tumor recurrence might be independent of surgical access; this strengthens the effectiveness of MI surgery.

Further research with longer follow-up is needed to compare long-term variables such as tumor recurrence.

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Table 1. Criteria for quality assessment.

Quality checklist
Selection
1. Assignment for treatment – any criteria reported? (If yes, 1-star)
2. How representative was the 'reference' group (MI) in comparison to the 'alternative' group (MS); (If yes, 1 star, no star i
Comparability
Comparability variables: (1) age; (2) gender; (3) renal function; (4) extracardiac arteriopathy; (5) poor mobility; (6) previou
3. Groups comparable for 1, 2, 3, 4, 5, 6, 7, 8, 9 (If yes, 1-star was assigned for each of these. No star was assigned if the gr
4. Groups comparable for 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 (If yes, 1-star was
assigned for each of these. No star was assigned if the two groups differed).
Outcome assessment
6. Clearly defined outcome of interest (If yes, 1-star).
7. Follow-up (1-star if described).
BSA=Body surface area. CCS= Canadian Cardiovascular Society. IDDM=insulin dependent diabetes mellitus; MI= minim

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Author, year (total patients) study type	MI/MS (N)	Age (y/o)	Age (y/o)	Sex (female) (no, %)	Sex (female) (no, %)	Sex (female) (no, %)	Sex (female) (no, %)	BSA(m2) BMI (kg/m2)	BSA(m2) BMI (kg/m2)	Tumor Size (max diameter cm)	Tumor Size (max diameter cm)	T F c a I
		MI	**MS**	**MI**	**MI**	**MI**	**MS**	**MI**	**MS**	**MI**	**MS**	**M**
Ravikumar 2000 (n=5) Retrospective	2/3	33.5	43.3	2 (100)	2 (100)	2 (100)	2 (66.3)	NA	NA	NA	NA	M 2 (

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Iribarne, 2010 (n=74) Retrospective	38/36	52.4±2.8	59.9±2.6	29 (76.3)	29 (76.3)	29 (76.3)	23 (63.8)	26.5±1	26.7±0.8	8.5±1.7	13.2±2.6	I a 1 (F a 1 (A (C (M o (F l f (T b (V l r r 4 (C 3 (

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Pineda, 2014 (n=39) Retrospective	22/17	62±17	57±12	18 (81.8)	18 (81.8)	18 (81.8)	12 (70.6)	NA	NA	7.5 (4-19.7)	7.5 (4-19.7)	I a 2 (A v (P a 6 (I v c (P v c (M c (P l f (T b (
Shilling, 2012 (n=45) Retrospective	16/29	53.1±15.2	58.8±11.4	58.8±11.4	11 (69)	21 (72)	21 (72)	34.6±6.8	28.6±5.3	NA	NA	I a 1 (M c (
Yang, 2015 (n=93) Retrospective	49/44	47.7±13	51.2±12.1	51.2±12.1	25 (51)	26 (59)	26 (59)	23.2±3.6	23.5±3.8	4.8	4.3	I a 4 (P a 4 (M c (

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Sawaki, 2015 (n=23) Retrospective	7/16	68.7±7.8	62.6±18.1	62.6±18.1	3 (43.3)	12 (75%)	12 (75%)	23.4±2.4	23.9±4.1	16±9	16.7±8.9	I a 6 (P a 1 (M c (
Lee, 2016 (n=146) Retrospective	63/83	51.5±14.6	54.8±13.9	54.8±13.9	54 (86)	51 (61)	51 (61)	23±2.9	23.1±2.7	3.7±1.8	3.5±1.5	I a 6 (P a 3 M c (
Moss, 2016 (n=69) Retrospective	30/39	55.1±13.1	59.5±13.4	59.5±13.4	23 (76.7)	27 (69.2)	27 (69.2)	29±7.5	28.6±6.1	NA	NA	I a 3 (

Table 2 Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**Table 2** Study characteristics	**T 2** S characterist
Dong, 2018 (n=66) Retrospective	30/36	56±6.5	53.9±5.9	53.9±5.9	24 (80)	27 (75)	27 (75)	21.7±1.8	22.6±2.1	44.5±2.7	45.9±3.6	I a 3 (M c (
Ellouze, 2018 (n=43) Retrospective	20/23	61±12	56±12	56±12	14 (70)	14 (61)	14 (61)	26±4	25±6	3.8±1.8	4.1±1.9	I a 1 (P a 2 (
Lou, 2019 (n=50) Retrospective	17/33	55.9±18.2	54.4±17.3	54.4±17.3	12 (70.6)	19 (57.6)	19 (57.6)	NA	NA	NA	NA	I a 4 (P a 8 (I v c (P v c (M c (I 2 P c c (P b 1

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Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	Data are presented as mean±SD or number. BMI=body mass index. BSA= body surface area. MI=Minimally invasive. MS=Median sternotomy.	D a p s a m o n b B m i d B b s f a M i s M s

Table 3. Overall results of meta-analysis

Outcome
Primary outcome
Late mortality
Late relapse
Secondary outcome
Early mortality[¶]
Bleeding
Respiratory failure
Renal failure
Neuro Complication
Length of stay[a]
CPB time[a]
Cross clamp time[a]
Late redo-surgery
Tumor size
CI=Confidence interval. CPB=Cardiopulmonary bypass. IRR=Incidence rate ratio. MI=Minimally invasive. MS=Median s

Glossary of abbreviations

CC Cross clamp

CI Confidence interval

CPB Cardiopulmonary bypass

IRR Incidence rate ratio

LoS Length of hospital stay

MI Minimally invasive

MS Median sternotomy

Figures legend

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Figure 2 A. Forest plot of the primary outcome late survival.**2B** . Forest plot of the primary outcome tumor relapse.

Figure 3. Risk of bias analysis.

Supplementary Figure 1. High quality studies**.** Forest plot of the primary outcome late survival.

Supplementary Figure 2. High quality studies**.** Forest plot of the primary outcome tumor relapse.

Supplementary Figure 3. Funnel plot primary outcome late survival.

Supplementary Figure 4 . Funnel plot primary outcome tumor relapse.

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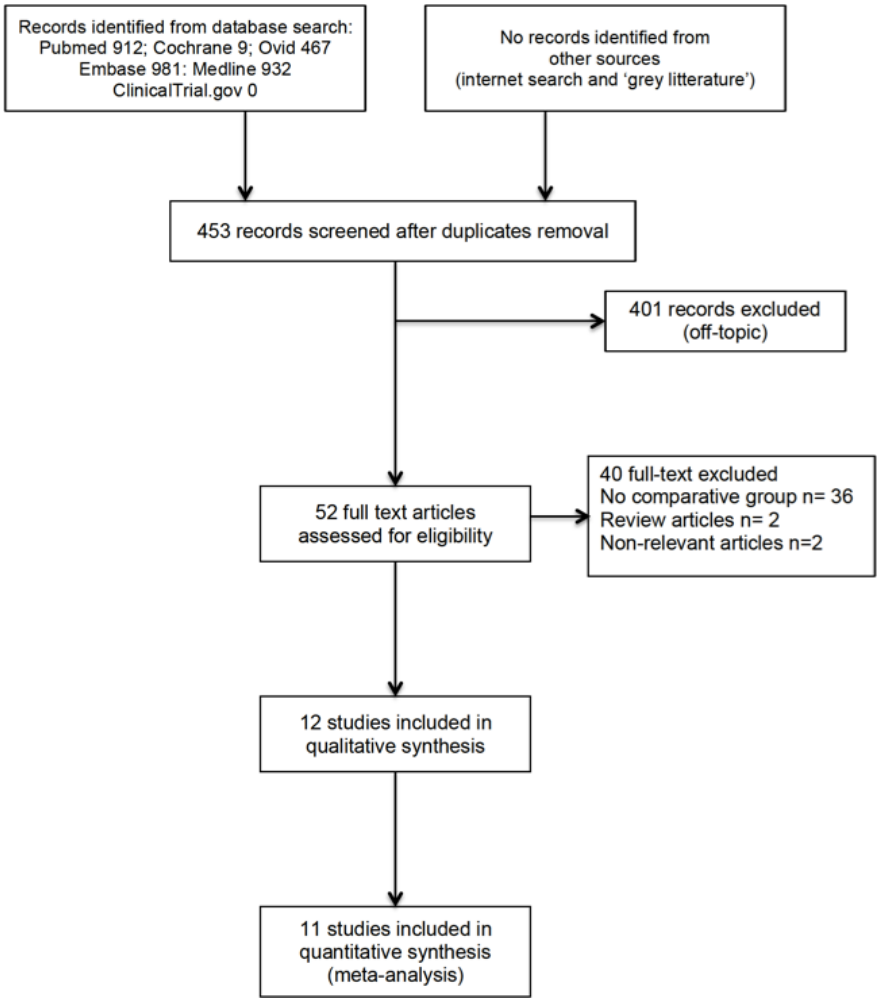
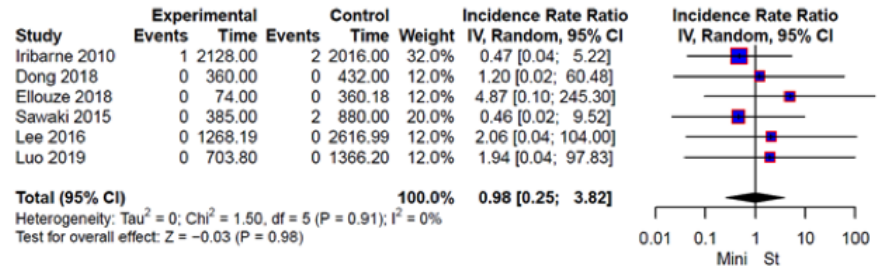


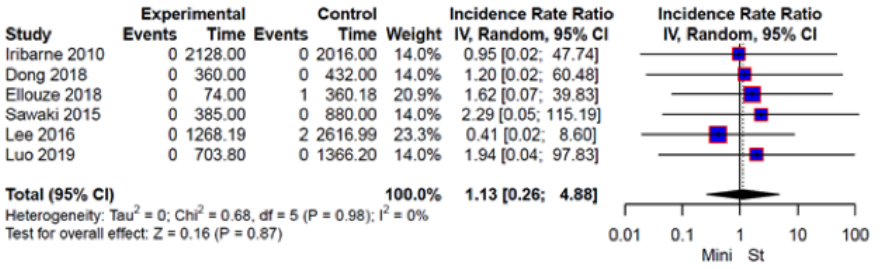
Late mortality



Study	Experimental Events	Experimental Time	Control Events	Control Time	Weight	Incidence Rate Ratio IV, Random, 95% CI
Iribarne 2010	1	2128.00	2	2016.00	32.0%	0.47 [0.04; 5.22]
Dong 2018	0	360.00	0	432.00	12.0%	1.20 [0.02; 60.48]
Ellouze 2018	0	74.00	0	360.18	12.0%	4.87 [0.10; 245.30]
Sawaki 2015	0	385.00	2	880.00	20.0%	0.46 [0.02; 9.52]
Lee 2016	0	1268.19	0	2616.99	12.0%	2.06 [0.04; 104.00]
Luo 2019	0	703.80	0	1366.20	12.0%	1.94 [0.04; 97.83]
Total (95% CI)					**100.0%**	**0.98 [0.25; 3.82]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.50$, df = 5 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = −0.03 (P = 0.98)

Late relapse



Study	Experimental Events	Experimental Time	Control Events	Control Time	Weight	Incidence Rate Ratio IV, Random, 95% CI
Iribarne 2010	0	2128.00	0	2016.00	14.0%	0.95 [0.02; 47.74]
Dong 2018	0	360.00	0	432.00	14.0%	1.20 [0.02; 60.48]
Ellouze 2018	0	74.00	1	360.18	20.9%	1.62 [0.07; 39.83]
Sawaki 2015	0	385.00	0	880.00	14.0%	2.29 [0.05; 115.19]
Lee 2016	0	1268.19	2	2616.99	23.3%	0.41 [0.02; 8.60]
Luo 2019	0	703.80	0	1366.20	14.0%	1.94 [0.04; 97.83]
Total (95% CI)					**100.0%**	**1.13 [0.26; 4.88]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.68$, df = 5 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.16 (P = 0.87)