The effect of intravenous milrinone in adult critically ill patients: a meta-analysis of randomized clinical trials

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Abstract

Background

Milrinone is widely used for enhancing myocardial contractility, however, there is inadequate data to suggest it is preferable to other inotropic agents. To observe the effect of milrinone on prognosis in adult critically ill patients, we conducted this meta-analysis.

Methods

A search of the following databases was conducted: Medline, Elsevier, Cochrane Central Register of Controlled Trials and Web of Science databases, and eligible randomized controlled trials including adult critically ill patients were screened. Two reviewers collected data separately, information was retrieved including study design, center number, sample size, gender, age, intervention and outcome. Data were analyzed using methods recommended by the Cochrane Collaboration Review Manager 4.2 software. Random errors were evaluated by trial sequential analysis (TSA).

Results

Twenty studies including 2036 patients compared milrinone with control group were enrolled. When compared to control group, the incidence of ventricular arrhythmia decreased significantly in milrinone group in patients with cardiac surgery, but not in patients with cardiac dysfunction and shock. There was no significant reduction in the incidence of myocardial infarction, all-cause mortality and no improvement of hemodynamic paramenters in the milrinone group. TSA indicated lack of firm evidence for a beneficial effect.

Conclusions

The meta-analysis showed when compared with control group, the incidence of ventricular arrhythmia decreased significantly in patients with cardiac surgery, but not in patients with cardiac dysfunction and shock who applying milrinone, while there was no significant reduction in the incidence of myocardial infarction, all-cause mortality and no improvement of hemodynamics.

Background

Cardiac dysfunction is a common life-threatening organ malfunction in critically ill patients, especially once it has progressed to shock[1, 2]. In order to stabilize patients, positive inotropic medications are commonly utilized to increase cardiac output. However, studies have failed to show that inotropes have a positive impact on outcomes[3], since they can cause adverse effects such as arrhythmias and myocardial ischemia. There is insufficient data to determine which inotropic is preferred to another[4].

Dobutamine is a synthetic catecholamine with beta receptor agonism that can raise cardiac output and blood pressure. However, its effects on tachycardia and increased myocardial oxygen consumption have limited its use. Milrinone is a phosphodiesterase-III inhibitor that improves cardiac inotropy and lusitropy by causing peripheral vasodilation. It is used to treat pulmonary hypertension and right ventricular dysfunction in patients. A retrospective cohort study using a national dataset showed milrinone were relatively safe at low dose when compared with other inotropics[3]. However, the most recent DOREMI study[5] evaluated dobutamine with milrinone in patients with cardiogenic shock and found no substantial benefit of milrinone over dobutamine for the key composite outcome, but the trial's single-center design limits its external generalizability.

Current data on the use of milrinone has significant risks of bias and random error, according to a meta-analysis done by Koster[6] on patients with cardiac dysfunction. Karami[7] did another meta analysis in which he examined vasopressors and inotropes in acute myocardial infarction-induced cardiogenic shock, only one study reported mortality and 50 patients treated with milrinone. To observe the effect of milrinone in critically ill adult patients, especially in patients with cardiac dysfunction or cardiac surgery, we conducted this meta-analysis.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PRISMA guidelines. The protocol was registered in the PROSPERO database (CRD42022329709).

Search strategy for identification of relevant studies

A search of the following databases was conducted: Medline, Elsevier, Cochrane Central Register of Controlled Trials and Web of Science databases. The following keywords were used as searching terms: milrinone or primacor or corotrope. No language restrictions were placed on the search. All databases were searched for articles published from inception until April 22, 2022. Additional files and supplementary appendices of the relevant articles were also reviewed. Detailed search strategies are shown in Additional File 1 - Search strategy.

Study selection

The full-text articles of all possibly acceptable studies were collected after one reviewer assessed the search results. The articles were then independently examined by two reviewers in compliance with the inclusion criteria. Consensus and discussion with a third reviewer were used to resolve disagreements

between the two reviewers. When the issue of "same author" or "same data" was raised, the most recent published study was included.

Inclusion and exclusion criteria

Trials with the following characteristics were included:

1. Randomized controlled trials.
2. Adult critically ill patients, especially patients with cardiac dysfunction or with cardiac surgerry are the target population.
3. Intervention: Milrinone was administered intravenously to the patients, with no restrictions on dose and duration.
4. Other drugs, such as placebo, dobutamine, and levosimendan, are compared.
5. Primary outcome: the incidence of ventricular arrhythmia, myocardial infarction or mortality from any cause were reported.

Trials with the following features were excluded:

1. They did not compare milrinone with other drugs.
2. Milrinone was administered by other route, including oral and/or inhaled route, which were inappropriate for critically ill patients.
3. They included no data on primary outcome.
4. Full-text articles were not available.

Quality assessment

Two reviewers independently assessed the quality of the studies, the disagreement was resolved by consulting a third reviewer. The trial's quality was determined using the 5-point Jadad scale[8]. Randomization, blinding, and loss to follow-up are all included on this scale. To assess the possibility of bias, sequence generation, allocation concealment, inadequate outcome data, selective reporting, and other bias were also examined. The latter was classified as low risk, unclear risk, or high risk for each trial. In all areas, low risk was defined as low risk of bias in all domains. Unclear risk was defined as unclear risk of bias in at least one area with no high risk of bias domains. High risk was defined as high risk of bias in one or more domains.

Data extraction and management

Two reviewers collected data separately using a data extraction table. Disagreements that arose twice were handled by discussing with another reviewer until a solution was found. Another reviewer then proofread the data. Other information was retrieved, including study design, center number, sample size, gender, age, intervention, outcome, ICU and hospital stay.

Statistical analysis

Review Manager 4.2 was used to assess the data (The Nordic Cochrane Center, Rigshospitalet, Copenhagen, Denmark). With 99% confidence intervals (CIs), the relative risk for dichotomous data and mean differences for continuous data was estimated. The I^2 test was used to assess and quantify the statistical heterogeneity of the data. $P < 0.05$ was used to determine heterogeneity. None, low, moderate, and high thresholds were defined as I^2 values of 0 - 24.9%, 25 - 49.9%, 50 - 74.9%, and 75-100%, respectively[9, 10]. If there was heterogeneity, we used the randomized-effects model[11]; otherwise, we used the fixed-effects model. Sensitivity analyses were used to assess the considerable heterogeneity. The two-sided p value of 0.05 was used to determine statistical significance.

The mean ± standard deviation was used to depict continuous data. The ICU and hospital length of stay, on the other hand, was presented as a median and interquartile range. To maintain the consistency of data, median instead of mean, and standard deviation was calculated by interquartile range divided by 1.35[12].

With the type-I errors resulting from an increased risk of error and repeated significance testing, and in order to combine information size estimation with an adjusted threshold for statistical significance in the meta-analysis, trial sequential analysis (TSA; TSA software version 0.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) was used. The relative risk reduction of the intervention in the included trials was used to determine information size as diversity-adjusted information size.

Results

Study location and selection

During the initial search, 4920 records were found, with 667 records being deleted as duplicates. The remaining 4253 records were then screened. 4144 articles were eliminated after titles and abstracts were reviewed. Figure 1 illustrates the flow diagram. There were 109 potentially suitable studies identified, 89 of which were eliminated, leaving 20 studies [5, 13–31] to be recruited. Details of the studies and reason for exclusion are shown in Additional file 2 - Excluded articles.

Study Characteristics

The features of the included studies are shown in Table 1. There were 2036 patients in the meta-analysis, 1033 in the milrinone group and 1003 in the control group. Four of the trials [13, 14, 18, 19] were multi-center studies, while the others were single-center studies. Seven trials [5, 13, 14, 17, 19, 21, 29] involved patients with cardiac dysfunction or shock, whereas the others enrolled patients undergoing heart surgery. In 13 trials [13, 14, 15, 16, 18, 22, 24, 25, 27, 28, 29,

30, 31], milrinone was given 30–75μg/kg intravenously as loading dose, then followed by infusion at the rate of 0.25-1.0 μg/kg/min, whereas milrinone was given without loading dose in the other trials.

Table 1
General characteristics of the studies included for comparison the effect of intravenous milrinone and dobutamine

Author year	Design	Center	Patient	Sample size		Sex (male/female)		Age		Intervention
				Milrinone	Control	Milrinone	Control	Milrinone	Control	Milrinone
Biddle 1987[1]	Randomized, open-label trial	5	Patients with stable NHYA class III or IV CHF.	40	39	35/5	36/3	61	60	Milrinone: loading dose of 50 or 75 ug/kg, followed by continuous infusion of 0.5-1.0 µg/kg.min.
Karlsberg 1996[2]	Randomized, open-label, parallel trial	6	Patients with CHF following AMI.	16	14	10/6	8/6	60 ± 3.4	66 ± 2.3	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0.25–0.75 µg/kg.min.
Doolan 1997[3]	Randomized, double-blinded placebo-controlled trial	1	Patients with left ventricular ejection fraction ≤ 35% and/or MPAP ≥ 20 mmHg before withdrawal of cardiopulmonary bypass.	15	15	14/1	14/1	65 ± 10.4	67 ± 8.6	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min.
Hamada 1999[4]	Randomized, controlled trial	1	Patients for elective cardiac surgery, 22 CABG and 8 prosthetic valve replacement.	10	20	6/4	13/7	66.2 ± 8.1	Amrinone 66.1 ± 11 Controls 62.4 ± 6.5	Milrinone: loading dose of 50µg/kg.
Siostrzonek 2000[5]	Randomized, open-label trial	1	Mechanically ventilated ICU patients with catecholamine-dependent heart failure.	10	10	3/7	4/6	58 ± 15	66 ± 9	Milrinone: continuous infusion of 0 µg/kg.min added to catecholami therapy.
Feneck 2001[6]	Randomized, open-label trial	6	Patients with low cardiac output after cardiac surgery.	60	60	33/27	38/22	63.9 (1.2)	64.4 (1.1)	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min.

N/A, not applicable. Values are expressed as mean (standard deviation) or median (interquartile range).

a. Acute myocardial infarction (AMI)

b. Congestive heart failure (CHF).

c. New York Heart Association (NHYA).

d. Coronary artery bypass grafting (CABG)

e. Central venous pressure (CVP)

f. Offpump coronary artery bypass graft (OPCAB)

g. Mean arterial pressure (MAP)

h. Mean pulmonary artery pressure (MPAP).

Author year	Design	Center	Patient	Sample size		Sex (male/female)		Age		Intervention
Cuffe 2002[7] OPTIME-CHF study	Randomized, double-blinded placebo-controlled trial	78	Patients with left ventricular ejection fraction < 40%, who requiring inotropic therapy (eg, for shock, metabolic acidosis, or severe hypotension).	477	472	306/171	371/101	66 (14)	65 (15)	Milrinone: continuous infusion of 0 µg/kg.min.
Möllhoff 2002[8]	Randomized, double-blinded trial	1	Hemodynamically stabe patients with left ventricular function < 40%, and scheduled for elective CABG surgery.	15	15	14/1	11/4	62 ± 12	68 ± 7	Milrinone: continuous infusion of 0.375 µg/kg.min.
Aranda 2003[9]	Randomized, open-label trial	1	Patients with heart failure awaiting cardiac transplantation who requiring inotropic therapy.	19	17	10/7	17/2	61 ± 8	54 ± 9	Milrinone: continuous infusion of 0.25 µg/kg.min, then titrated by 0.125–0.1 µg/kg.min.
Al-Shawaf 2006[10]	Randomized open-label trial	1	Type 2 diabetic patients undergoing elective surgery for coronary artery disease.	16	14	15/2	13/1	58 ± 10	61 ± 11	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0.3–0.5 µg/kg.min.
Lee 2006[11]	Randomized open-label trial	1	Patients scheduled for OPCAB with right ventricular ejection fraction < 35%.	24	26	20/4	20/6	63 ± 8	62 ± 8	Milrinone; continuous infusion of 0 µg/kg.min throughout t OPCAB procedures.
Brackbill 2007[12]	Randomized, open-label trial	1	Hemodynamically stable patients with ejection fractions ≤ 35% undergoing CABG surgery.	20	20	16/4	17/3	62.1 ± 15.1	65.8 ± 11.8	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0.375 µg/kg.min.

N/A, not applicable. Values are expressed as mean (standard deviation) or median (interquartile range).

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Author year	Design	Center	Patient	Sample size		Sex (male/female)		Age		Intervention
Couture 2007[13]	Randomized open-label trial	1	Patients undergoing CABG with left ventricular diastolic dysfunction.	25	25	19/6	19/6	67 ± 8	70 ± 7	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min.
De Hert 2007[14]	Randomized, observer-blinded trial	1	Patients with ejection fraction ≤ 30% scheduled for elective cardiac surgery with cardiopulmonary bypass.	15	15	10/5	10/5	69 ± 10	67 ± 11	Milrinone: continuous infusion of 0 mg/kg.min.
Jebeli 2010[15]	Randomized, double-blind, placebo controlled trial	1	Patients with left ventricular ejection fraction < 35% undergoing CABG.	35	35	25/10	28/7	56.9 ± 9.7	58.2 ± 8.4	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min fo 24 hours.
Hadadzadeh 2013[16]	Randomized, double-blind, placebo controlled trial	1	Patients with ejection fraction < 35% scheduled for elective OPCAB.	40	40	31/9	26/14	61.9 ± 10.71	63 ± 9.6	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min.
Wang 2015[17]	Randomized, non-blinded study	1	Patients with severe sepsis.	60	30	38/22	20/10	38 (20–57) 34 (21–60)	33.5 (23–60)	Milrinone: loading dose of 30 ug/kg, followed by continuous infusion of 0.375-0.5 µg/kg.min.
Mishra 2016[18]	Randomized open-label trial	1	Patients undergoing valve replacement with pulmonary artery hypertension and left ventricular dysfunction.	20	20	N/A	N/A	43.7 ± 13.1	37.3 ± 11.7	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0 µg/kg.min fo 24 hours.

N/A, not applicable. Values are expressed as mean (standard deviation) or median (interquartile range).

a. Acute myocardial infarction (AMI)

b. Congestive heart failure (CHF).

c. New York Heart Association (NHYA).

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g. Mean arterial pressure (MAP)

h. Mean pulmonary artery pressure (MPAP).

Author year	Design	Center	Patient	Sample size		Sex (male/female)		Age		Intervention
Eskandr, 2018[19]	Randomized, double-blinded, controlled study	1	Patients had systolic pulmonary arterial pressure ≥ 60 mmHg and were scheduled for elective mitral valve replacement.	20	20	7/13	6/14	29.7 ± 3.8	28.5 ± 3.7	Milrinone: loading dose of 50 ug/kg, followed by continuous infusion of 0.25–0.75 μg/kg.min.
Mathew 2021[20] DOREMI study	Randomized, double-blind trial	1	Patients had cardiogenic shock stage B, C, D, or E.	96	96	60	62	68.9 ± 13.8	72.0 ± 11.3	Milrinone: continuous infusion of 0.125, 0.250 0.375, 0.500 0.500 μg/kg.min fo stage 1–5.
N/A, not applicable. Values are expressed as mean (standard deviation) or median (interquartile range).										
a. Acute myocardial infarction (AMI)										
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h. Mean pulmonary artery pressure (MPAP).										

Except for one [5], almost all the trials were assessed as high risk of bias. Quality assessment is shown in Fig. 2. Six trials [5, 17, 25, 26, 29, 30] had a low risk of bias when it came to sequence generation, seven trials [5, 22, 23, 25, 26, 30, 31] had a low risk of bias regarding allocation concealment, five trials [5, 15, 23, 25, 31] had a low risk of bias regarding blinding of participants, and five trials [5, 15, 19, 26, 30] had a low risk of bias regarding blinding of outcome assessment.

The effects of milrinone on ventricular arrhythmia and myocardial infarction

Milrinone's effects on the incidence of ventricular arrhythmia were calculated using data from 15 trials (Fig. 3). The incidence of ventricular arrhythmia was not significantly different between groups in patients with cardiac dysfunction ($p = 0.54$, $I^2 = 22\%$), however, the incidence decreased significantly in the milrinone group in patients with cardiac surgery ($p = 0.03$, $I^2 = 0\%$).

Milrinone had no benefit effect on the incidence of myocardial infarction in patients with cardiac dysfunction ($p = 0.07$, $I^2 = 0\%$) and cardiac surgery ($p = 0.91$, $I^2 = 57\%$) (Additional file 3- Figure A). Meanwhile, milrinone had no benefit effect on the use of intra-aortic balloon counterpulsation (IABP) when compared with control group in patients with cardiac dysfunction ($p = 0.54$, $I^2 = 0\%$) and cardiac surgery ($p = 0.20$, $I^2 = 0\%$) (Additional file 3 - Figure B).

The effects of milrinone on mortality

Milrinone's effects on mortality were calculated using data from 15 trials (Additional file 3 - Figure C), and heterogeneity was found ($p = 0.4$, $I^2 = 5\%$). Overall mortality was 98 of 884 (11.1%) and 87 of 842 (10.3%) in the milrinone and control groups, respectively. When compared to control group, there was no significant reduction in all-cause mortality in the milrinone group. Milrinone's effects on mortality were compared with dubutamine, levosimendan and saline (Additional file 3 - Figure D), the mortality was not significantly different between groups.

Meanwhile, there was no difference on hospital length of stay and ICU length of stay in milrinone and control group(Additional file 3 - Figure E).

The effects of milrinone on hemodynamics

There was no difference on heart rate after applying milrinone on 3 or 4 hours ($p = 0.51$, $I^2 = 62\%$) and 48 hours ($p = 0.43$, $I^2 = 27\%$) when compared with control group, however, there was a trend toward higher heart rate of milrinone group on 24 hours ($p = 0.06$, $I^2 = 46\%$) (Additional file 3 - Figure F).

There was no difference on pulmonary capillary wedge pressure after applying milrinone on 24 hours ($p = 0.26$, $I^2 = 29\%$) and 48 hours ($p = 0.87$, $I^2 = 80\%$) when compared with control group, however, pulmonary capillary wedge pressure of milrinone group was significantly lower on 3 or 4 hours ($p = 0.02$, $I^2 = 28\%$) (Additional file 3 - Figure G).

There was no difference on mean arterial pressure (Additional file 3 - Figure H) after applying milrinone or other inotropic agents on 3 or 4 hours, 24 hours and 48 hours.

Random errors

Trial sequential analysis was calculated with control event proportion of 12.7%,α = 0.05 and β = 0.20 (power 80%) to adjust for random error and recurrent testing of sparse data. The information size of 4927 has not been met (Fig. 4). Because the monitoring border was not crossed and the requisite information size was not obtained, trial sequential analysis indicated there was insufficient reliable and conclusive evidence for milrinone's favorable effect on mortality.

Discussion

The meta-analysis showed when compared with control group, the incidence of ventricular arrhythmia decreased significantly in patients with cardiac surgery, but not in patients with cardiac dysfunction and shock who applying milrinone, while there was no significant reduction in the incidence of myocardial infarction, all-cause mortality and no improvement of hemodynamics.

These results were quite different with other studies. Lewis[32] conducted a retrospective review in 100 cardiogenic shock patients, and found milrinone was more commonly discontinued due to hypotension while dobutamine was more commonly associated with arrhythmia. But the study limited the severity of the enrolled patients by excluding patients with IABP.

Our meta-analysis have some strengths. We did an integrated comparison of mirinone with different control group on different population and outcome. Since inotropics are used to increase cardiac output, but sometimes induce side effects of arrhythmias and myocardial ischemia, the comparison of ventricular arrhythmias and myocardial ischemia, mortality and hospital length of stay, as well as hemodynamics including heart rate, mean arterial pressure and pulmonary capillary wedge pressure were perfomed. Some meta analysis compared milrinone with controls in patients with cardiac dysfunction. Karami[7] found insufficient evidence supporting milrinone associated with reduced mortality in patients with myocardial infarction related cardiogenic shock, but including only 50 patients treated with milrinone. Biswas[33] did a meta-analysis which including 10 studies with 21,106 patients, and found milrinone had advantage over dobutamine in patients with acute decompensated heart failure and cardiogenic shock, however, only one randomized controlled trial was included, limiting the definite benefit of milrinone.

Limitations

There are some limitations of the meta analysis. Firstly, almost all the trials were assessed as high risk of bias, and only four studies were multicenterr studies, the low quality of study decease the reliability of the results. Secondly, the dosage of milrinone were different, loading dose were given in 13 trials, while no loading dose with different maintenance were used in the left studies.

Conclusion

The meta-analysis showed when compared with control group, the incidence of ventricular arrhythmia decreased significantly in patients with cardiac surgery, but not in patients with cardiac dysfunction and shock who applying milrinone, while there was no significant reduction in the incidence of myocardial infarction, all-cause mortality and no improvement of hemodynamics. However, TSA indicated lack of firm evidence due to considerable heterogeneity between groups.

Abbreviations

CIs
confidence intervals
IABP
intra-aortic balloon counterpulsation
TSA
trial sequential analysis.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions

JYX carried out the analysis and interpretation of data and participated in drafting, editing and submitting the manuscript. All of the articles were reviewed by two reviewers (JYX and YJZ) independently in accordance with the inclusion criteria. Disagreements between the two reviewers were resolved by consensus and discussion including a third reviewer (JJ). The quality of each article was assessed by JYX and YJZ independently. Disagreements were resolved by consulting a third reviewer (JJ). Using a data extraction table, JYX and YJZ independently extracted data. Disagreements were resolved by discussion with JJ until a consensus was achieved. YY contributed to the design and coordination of the study. FMG was responsible for conception and design, and revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

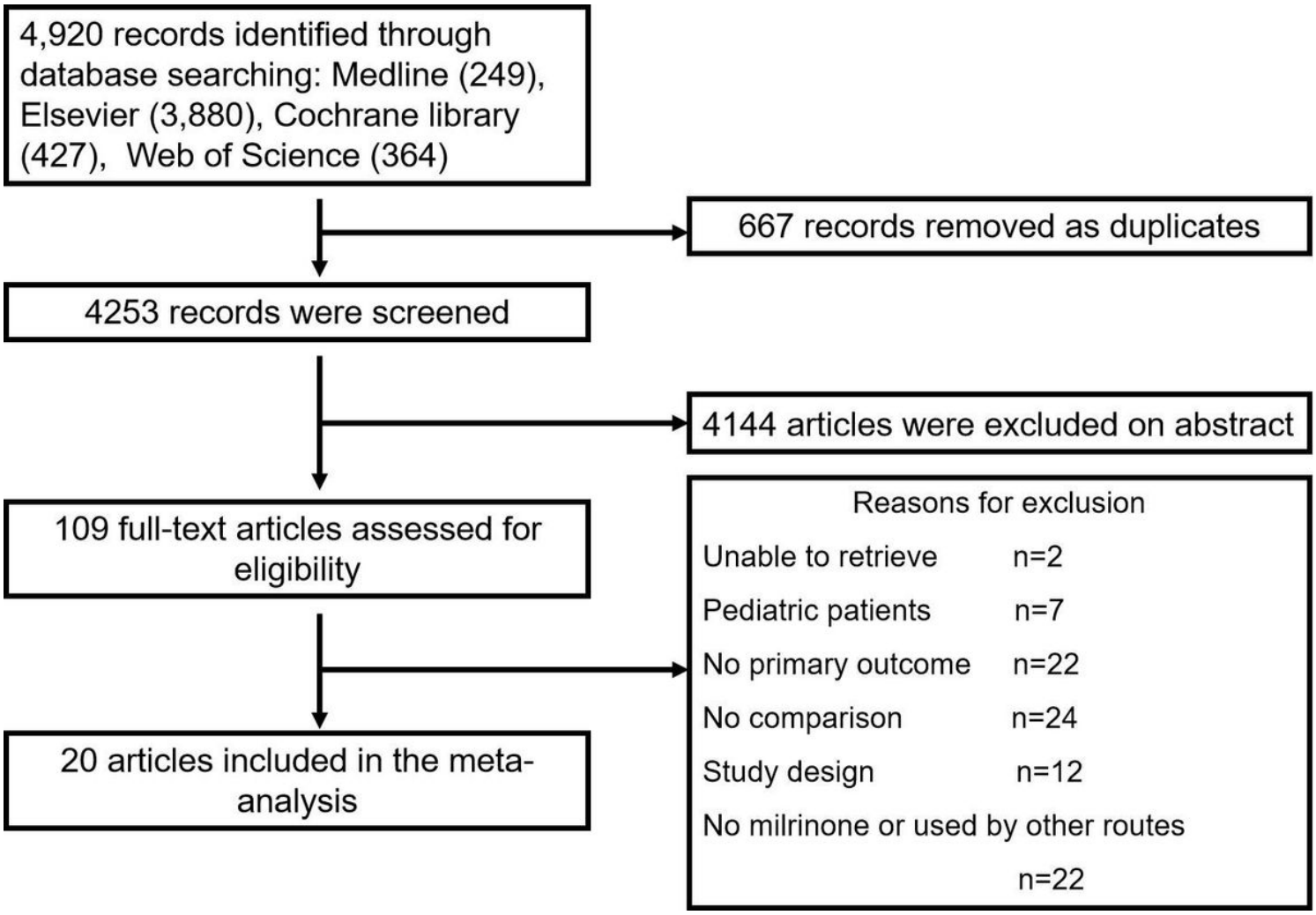

Figure 1

Flow diagram of the databases search.

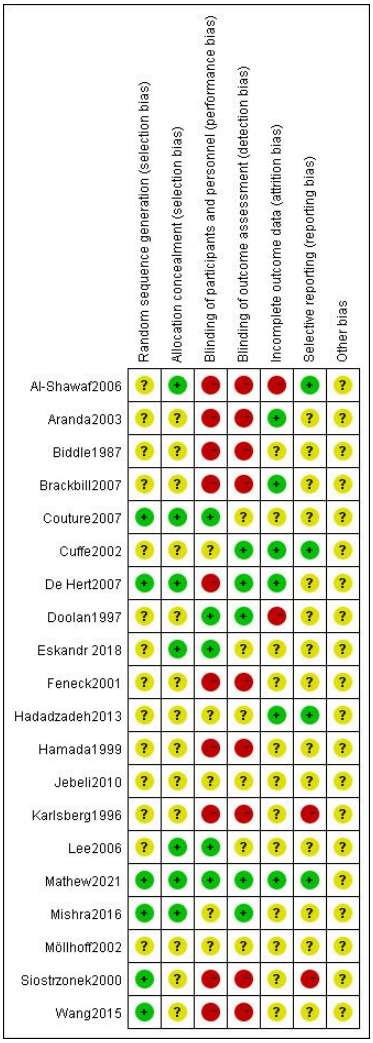

Figure 2

Risk of bias assessment.

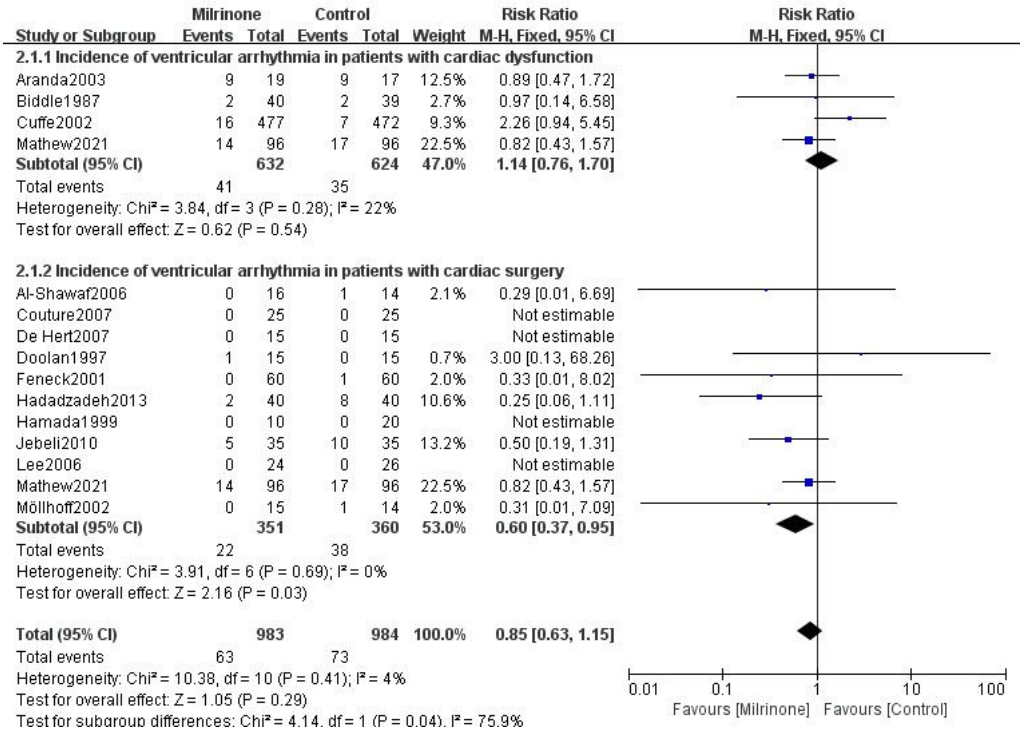

Figure 3

The effects of milrinone on the incidence of ventricular arrythmia.

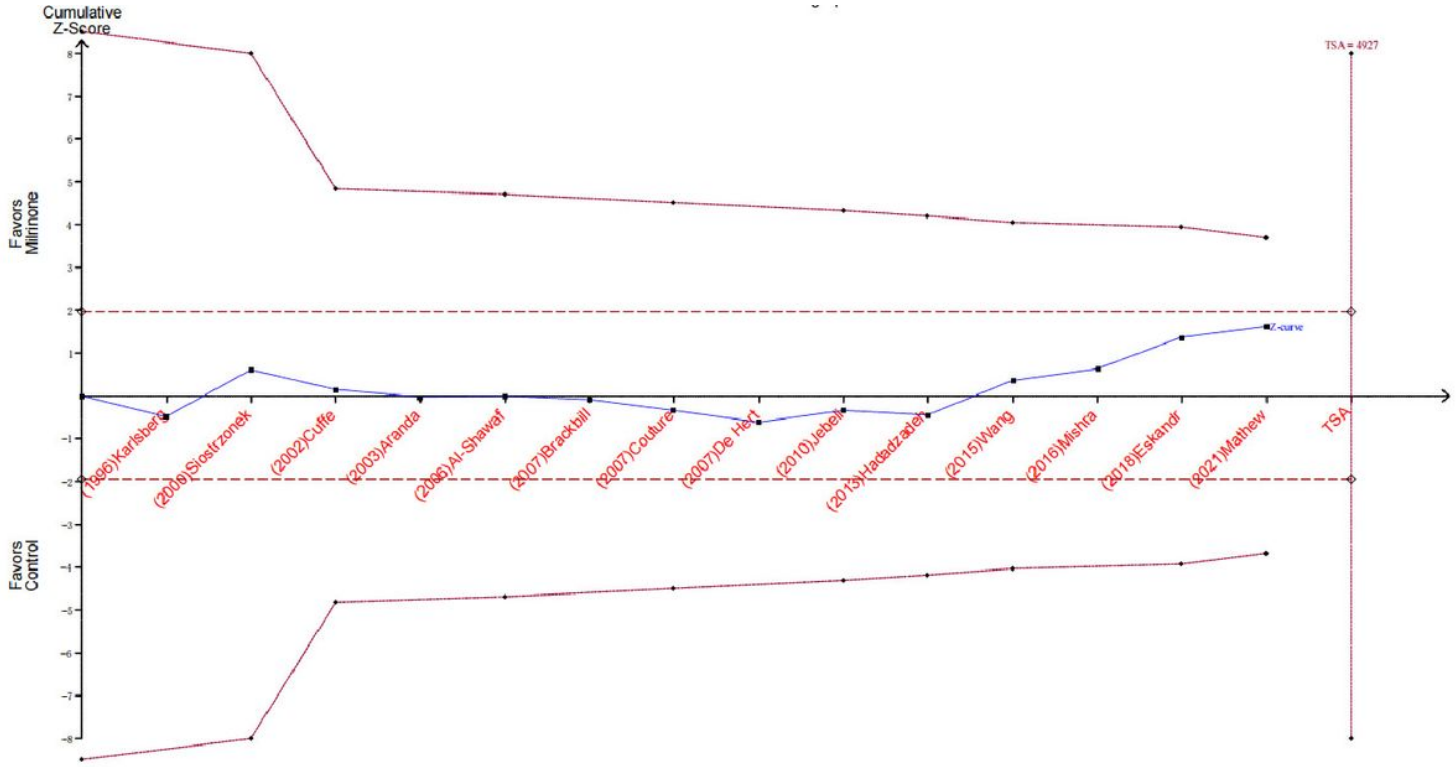

Figure 4

Trial sequential analysis of mortality with control event proportion of 12.7%,αof 5%, power of 80%, and a relative risk reduction of 20%. The information size of 4927 has not been reached.

Supplementary Files

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