

# Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis

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Intravenous morphine is a controversial treatment for acute heart failure (AHF). This study aimed to evaluate and compare the efficacy of intravenous morphine treatment vs. no morphine treatment in AHF patients. Relevant research conducted before June 2020 was retrieved from electronic databases. One unpublished study of our own was also included. Studies were eligible for inclusion if they compared AHF patients treated with intravenous morphine and patients who did not receive morphine. This meta-analysis included three propensity-matched cohorts and two retrospective analyses, involving a total of 149,967 patients (intravenous-morphine group,  $n = 22,072$ ; no-morphine group,  $n = 127,895$ ). There was a non-significant increase in the in-hospital mortality in the morphine group (combined odds ratio [OR] = 2.14, 95% confidence interval [CI]: 0.88–5.23,  $p = 0.095$ ,  $I^2 = 97.1\%$ ). However, subgroup analysis showed that the rate of in-hospital mortality with odds of 1.41 times more likely (95% CI: 1.11–1.80,  $p = 0.005$ ,  $I^2 = 0\%$ ) in those receiving vs. not receiving intravenous morphine. No significant correlation was found between intravenous morphine and invasive mechanical ventilation (OR = 2.19, 95% CI: 0.84–5.73,  $p = 0.10$ ,  $I^2 = 94.2\%$ ; subgroup analysis: OR = 2.24, 95% CI: 0.70–7.21,  $p = 0.176$ ,  $I^2 = 95.1\%$ ) or long-term mortality (hazard ratio = 1.15, 95% CI: 0.96–1.34,  $p = 0.335$ ;  $I^2 = 8.6\%$ ). The administration of intravenous morphine to patients with AHF may be related to in-hospital mortality, but not to invasive mechanical ventilation and long-term mortality.

## Keywords

Intravenous morphine; Acute heart failure; In-hospital mortality; Mechanical ventilation; Long-term mortality

## 1. Introduction

Acute heart failure (AHF) is defined as a sudden deterioration of cardiac function or the sudden onset of the symptoms and signs of heart failure [1]. AHF is a critical illness requiring prompt evaluation and treatment, as it typically leads to cardiogenic shock and is associated with a high risk of mortality [2]. For several decades, morphine

has been recommended for the improvement of severe pulmonary edema in AHF based on a class-IIb level of evidence [3, 4]. However, intravenous morphine has been reported to produce adverse effects, such as nausea, hypotension, myocardial depression, and brainstem/respiratory center suppression (which increases the need for mechanical ventilation), in patients with AHF, thereby increasing the risk of poor clinical outcomes [5–9]. Although morphine has long been used to treat AHF patients, no consensus has yet been reached on the potential mortality risk of patients receiving morphine treatment.

Therefore, we conducted this meta-analysis to evaluate and compare the clinical safety of intravenous morphine treatment in AHF patients.

## 2. Patients and methods

### 2.1 Search strategy

We performed a comprehensive search of relevant publications in the following electronic databases: PubMed, Google Scholar, and Cochrane Central Register of Controlled Trials. We searched for studies conducted before June 2020. The following search terms were used: “intravenous morphine”, “morphine”, “opioids”, “acute heart failure”, “heart failure”, and “pulmonary edema”. In addition, we evaluated related publications, including review articles and editorials. One unpublished study of our own was also included in this meta-analysis. The present study was registered at PROSPERO (CRD42020207805).

### 2.2 Study selection and data extraction

Included papers required fulfillment of the following content criteria: (i) patients with AHF, and (ii) intravenous morphine used in the treatment group (dosage  $\geq 0.5$  mg/kg) vs no morphine used in the control group. Studies were excluded if they examined heart failure that was chronic or accompanied

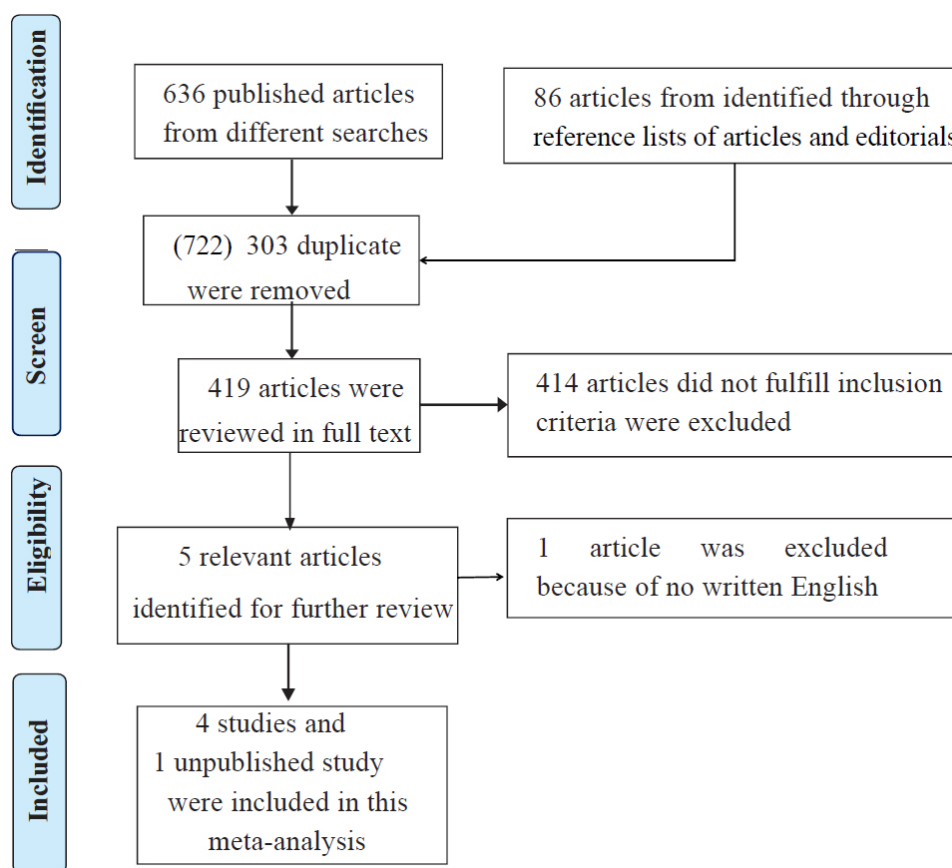


Fig. 1. Flow chart of the study-selection processes.

by sepsis or severe pneumonia; oral morphine use; palliative and end of life care. Only papers written in English were included, and case reports and case series were excluded. The study data was independently extracted by Lin and Chen using pre-defined extraction forms and conflict was resolved by a third reviewer.

### 2.3 Data analysis and risk of bias assessment

The primary endpoint was in-hospital mortality. The secondary endpoints were need for invasive mechanical ventilation and long-term mortality with follow-up durations ranging from 30 days to 12 months. We used the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the risk of bias of the included studies. The Begg's funnel plot was used to evaluate publication bias.

### 2.4 Statistical analysis

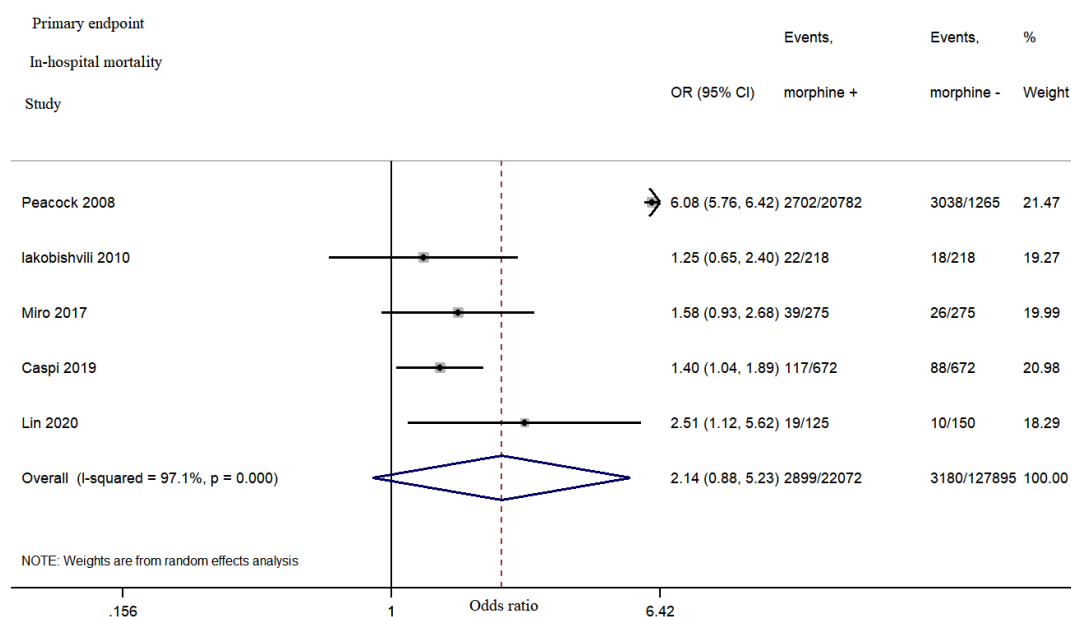
We used STATA software (version 14.0; StatCorp, College Station, TX, USA) to conduct the meta-analysis. The primary endpoint (in-hospital mortality) and secondary endpoints (invasive mechanical ventilation and long-term mortality) were calculated as combined odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CIs). The  $I^2$  statistic was used to assess heterogeneity between studies. If  $I^2 > 50\%$  (a random-effects model), subgroups (such as score-matching studies for the primary endpoint) were studied to

reduce the heterogeneity. Begg's funnel plots were used to assess publication bias. Statistical significance was set at  $p < 0.05$ .

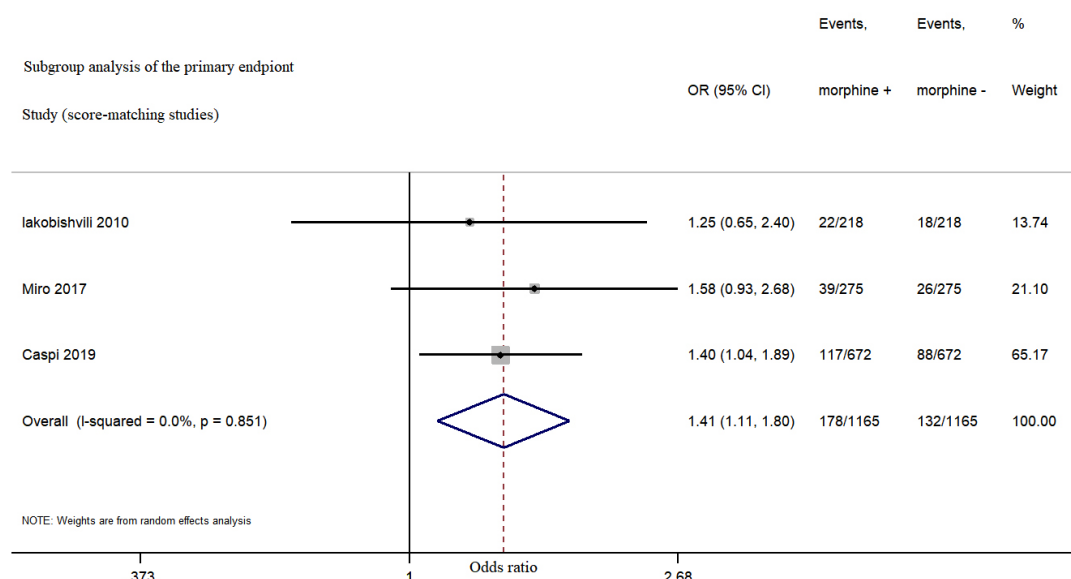
## 3. Results

### 3.1 Characteristics of included studies

Initial screening identified 722 related studies through the different search engines. Of these, we excluded 303 duplicated articles, 414 articles that did not fulfill the inclusion criteria, and 1 article that was not written in English. Thus, three propensity-matched cohorts [7–9] and one retrospective analysis [6] were included. Additionally, we included our own unpublished study, “Correlations between Morphine Use and Adverse Outcomes in Acute ST-Segment Elevation Myocardial Infarction with Acute Heart Failure: a retrospective study” which was a retrospective analysis available as a preprint on Research Square [10]. Thus, finally, a total of 149,967 patients were included (intravenous-morphine group,  $n = 22,072$ ; no-morphine group,  $n = 127,895$ ) as seen in Fig. 1. All studies provided the primary clinical endpoints, and 4 studies provided the secondary endpoint; 3 studies had follow-up durations ranging from 30 days to 12 months (Table 1, Ref. [6–10]).



**Fig. 2. Morphine use in acute heart failure was associated with a non-significant increase in the in-hospital mortality.**



**Fig. 3. Morphine use in acute heart failure increased in-hospital mortality from subgroup analysis.**

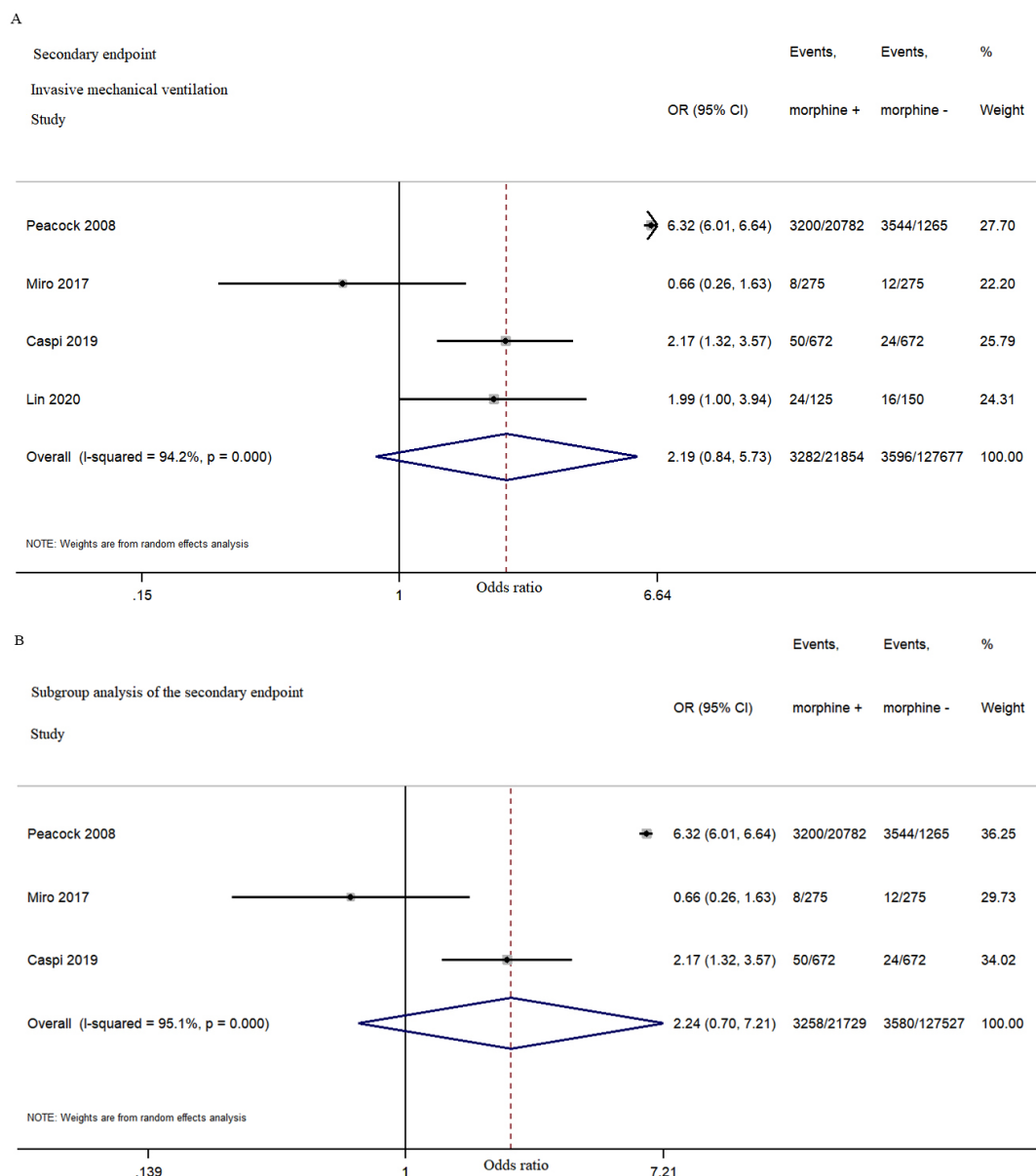
### 3.2 Primary and secondary endpoints

There was a non-significant increase in the in-hospital mortality in the morphine group (OR = 2.14, 95% CI: 0.88–5.23,  $p = 0.095$ ,  $I^2 = 97.1\%$ ; Fig. 2). However, as seen in Fig. 3, subgroup analyses (including score-matching studies only) revealed that in-hospital mortality for AHF patients receiving morphine was 1.41 times more likely (95% CI: 1.11–1.80,  $p = 0.005$ ,  $I^2 = 0\%$ ) compared to those not receiving morphine. In Fig. 4A, the secondary endpoint of needing mechanical ventilation is shown. Compared to no morphine treatment, intravenous morphine was not significantly related to a higher risk of invasive mechanical ventilation (OR = 2.19, 95% CI:

0.84–5.73,  $p = 0.10$ ,  $I^2 = 94.2\%$ , Fig. 4A). Subgroup analysis of the secondary endpoint (eliminate the study of Lin YW *et al.* [10] with AMI) also revealed no difference (OR = 2.24, 95% CI: 0.70–7.21,  $p = 0.176$ ,  $I^2 = 95.1\%$ , Fig. 4B). No significant correlation was found between long-term mortality and intravenous morphine (hazard ratio = 1.15, 95% CI: 0.96–1.34,  $p = 0.335$ ,  $I^2 = 8.6\%$ ; Fig. 5).

### 3.3 Risk-of-bias assessment and heterogeneity analysis

All included studies represented a low risk of bias in selective outcome reporting and outcome assessment. The scores of NOS for study quality assessment of included studies



**Fig. 4. Morphine use in acute heart failure did not significantly increased the rate of invasive mechanical ventilation during hospitalization.** (A) The second endpoint study of invasive mechanical ventilation during hospitalization. (B) The subgroup analysis of the second endpoint.

ranged from 7 to 9. However, the funnel plot asymmetry for in-hospital mortality and invasive mechanical ventilation indicated publication bias (Fig. 6). Between-study heterogeneity in in-hospital mortality was  $I^2 = 97.1\%$ . Accordingly, subgroup analyses including score-matching studies only were conducted, for which in-hospital mortality was  $I^2 = 0\%$ , suggesting low heterogeneity (Fig. 3).

#### 4. Discussion

This meta-analysis showed a trend for increased risk of in-hospital mortality in AHF patients who received intravenous morphine treatment as compared to AHF patients who were not treated with morphine from subgroup analysis.

Morphine can be a valuable treatment for AHF, especially

in patients with acute pulmonary edema, because of its anti-anxiety, vasodilator, pain-relieving, and sedative properties [11]. However, the American Heart Association/American College of Cardiology supports the use of morphine only for the palliative treatment of end-stage heart failure [12], while the European Society of Cardiology recommends the use of morphine only for patients with severe breathing difficulties or prominent pulmonary edema [2]. Morphine treatment in AHF has several potentially harmful effects, including vomiting (which leads to decreased drug absorption and an increased risk of apnea) [13], myocardial depression (which decreases the heart rate and cardiac output) [14, 15], respiratory depression (which increases the risk of invasive mechanical

**Table 1. General characteristics of studies included in this meta-analysis.**

Study	Year	Design	Participants	Primary endpoint (in-hospital mortality)	Secondary endpoint	Follow-up
Peacock WF, <i>et al.</i> [6]	2008	Retrospective analysis	Acute decompensated heart failure (a) morphine group, n = 20,782; EF% 35 (22, 50) (b) no-morphine group, n = 126,580; EF% 35 (23, 53)	2702 (13.0%) vs. 3038 (2.4%), $p = 0.001$	Mechanical ventilation 3200 (15.4%) vs. 3544 (2.8%), $p < 0.001$	-
Iakobishvili Z, <i>et al.</i> [7]	2010	Prospective heart failure survey (score-matching analysis)	Acute decompensated heart failure (a) morphine group, n = 218; EF% 35 (35, 42) (b) no-morphine group, n = 218; EF% 35 (25, 50)	22 (11.5%) vs. 18 (8.3%), $p = 0.55$	No data available	-
Miró O, <i>et al.</i> [8]	2017	Multicenter observational study (score-matching analysis)	Acute heart failure (a) morphine group, n = 275; NYHA III–IV% 32.1 (b) no-morphine group, n = 275; NYHA III–IV% 33.5	39 (14.2%) vs. 26 (9.1%), $p = 0.083$	Mechanical ventilation 8 (2.9%) vs. 12 (4.4%), $p = 0.5$ 30-day mortality OR = 1.66 (95% CI: 1.09–2.54)	30 days
Caspi O, <i>et al.</i> [9]	2019	Propensity matched cohort	Acute decompensated heart failure (a) morphine group, n = 672 (b) no-morphine group, n = 672	117 (17.4%) vs. 88 (13.4%), $p = 0.083$	Mechanical ventilation 50 (7.4%) vs. 24 (3.6%), $p = 0.003$ 12-month mortality OR = 1.11 (95% CI: 0.93–1.33), $p = 0.32$	12 months
Lin YW, <i>et al.</i> [10]	2020	Retrospective analysis	AMI with acute heart failure (a) morphine group, n = 125; EF% $49.74 \pm 10.75$ (b) no-morphine group, n = 150; EF% $49.39 \pm 9.66$	19 (15.2%) vs. 10 (6.67%), $p = 0.035$	Mechanical ventilation 24 (19.2%) vs. 16 (10.67%), $p = 0.031$ 12-month mortality OR = 1.54 (95% CI: 0.55–4.3), $p = 0.40$	12 months

AMI, acute myocardial infarction; OR, odds ratio; CI, confidence interval; HR, hazard ratio.

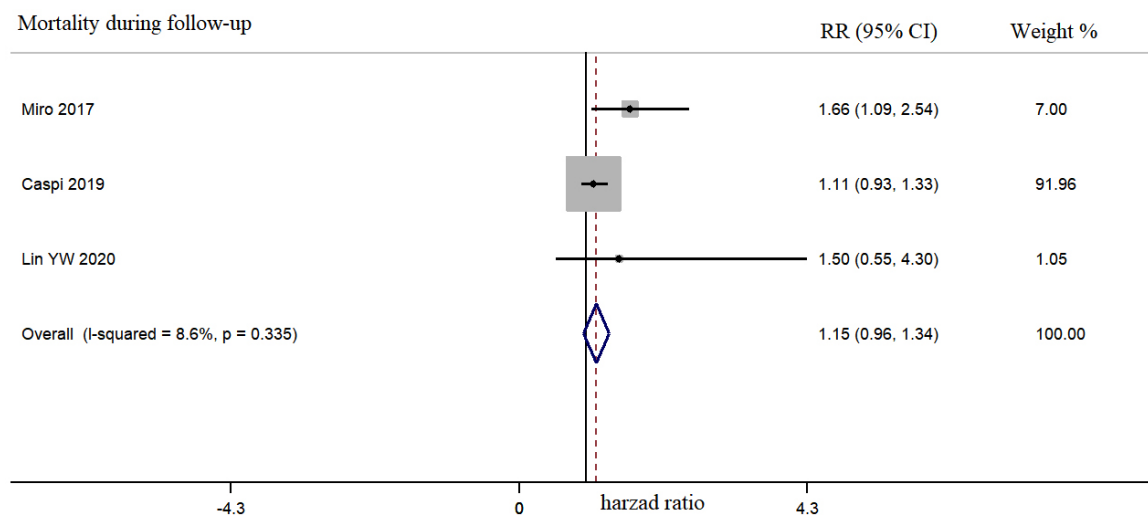


Fig. 5. Morphine use in acute heart failure was not associated with long-term mortality during a follow-up period of 30–365 days.

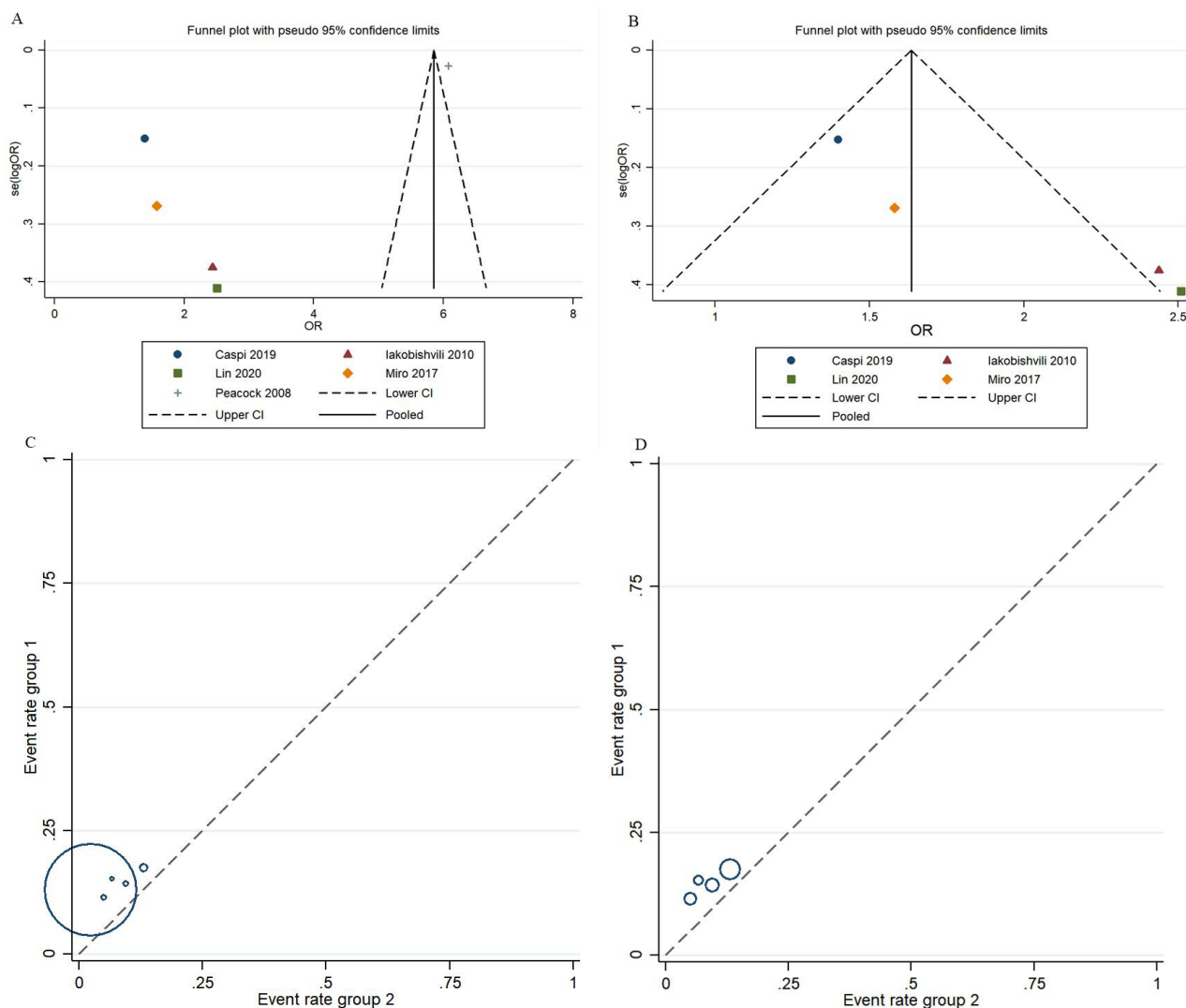
ventilation) [16–18], and attenuated platelet inhibition [19–21]. These adverse effects may increase the risk of death in patients receiving intravenous morphine.

Our meta-analysis showed a trend in the relationship between intravenous morphine treatment and in-hospital mortality in patients with AHF. Thus far, no randomized clinical trial has examined the benefit and safety of intravenous morphine in patients with AHF. In 2008, a review of five studies conducted between 1987 and 2003 showed that the use of morphine could worsen the condition of AHF patients [22]. Since then, the Acute Decompensated Heart Failure National Registry (ADHERE) trial has shown that compared to no morphine treatment, the use of intravenous morphine in acute decompensated heart failure was independently associated with a higher risk of in-hospital death (13.00% vs. 2.40%,  $p = 0.001$ ) [6]. However, Iakobishvili *et al.* [7] conducted propensity analysis and demonstrated that intravenous morphine was not associated with in-hospital death (OR = 1.2,  $p = 0.55$ ), except in the case of patients with Killip class III–IV acute myocardial infarction (OR = 2.3, 95% CI: 1.5–3.5). Similar results were obtained using a propensity score-matched analysis based on the Epidemiology of Acute Heart Failure in Emergency Departments Registry. Specifically, the results showed that intravenous morphine treatment not only significantly increased in-hospital mortality (14.2% vs. 9.1%, OR = 1.65,  $p = 0.083$ ), but was also significantly associated with 30-day mortality (20% vs. 12.7%, OR = 1.66,  $p = 0.017$ ) in patients AHF [8]. These findings suggest that morphine treatment tended to aggravate adverse outcomes, but this result was not obvious. In a recent study by Caspi *et al.* [9], morphine administration was associated with in-hospital mortality (17.4% vs. 13.4%, OR = 1.43,  $p = 0.024$ ) and showed a significant linear dose-response relationship with this outcome. The above results may be attributable to the adverse effects of intravenous morphine, which themselves depend on various factors such as morphine dosage, worse functional status,

and advanced heart failure (New York Heart Association class III–IV).

Our analysis demonstrated that intravenous morphine was not positively correlated with an increased risk of invasive mechanical ventilation and long-time mortality. As significant heterogeneity persisted after subgroup analysis, it was not clear whether morphine use led to endotracheal intubation or whether invasive mechanical ventilation required morphine use as a sedative (the timing of morphine use was unclear in the ADHERE trial) [6]. However, other retrospective studies have reported that morphine use does increase the risk of endotracheal intubation [23].

Potential limitations of our meta-analysis should be considered. First, the included studies were real-world observational and retrospective studies. Therefore, in some studies, there were differences at baseline between the subjects who received morphine and those who did not. Accordingly, the subgroup analysis including score-matching studies was conducted to reduce the risk of selective bias and heterogeneity. Second, the subgroup analysis of dosage of morphine was unavailable, and the temporal relationship between morphine use and adverse reactions was unknown. Third, myocardial infarction can by itself portend risk of mortality and confuse research results. Finally, limited data on mechanical ventilation were included in the literature analyzed (only 4 studies measured invasive mechanical ventilation during hospitalization, and one of them was not published), and the causal relationship between morphine and mechanical ventilation remains unclear. These factors could have created additional heterogeneity. Despite the above limitations, we believe that our study strengths include our well-designed and strict systematic review methodology. Randomized controlled trials are required to further confirm these results.



**Fig. 6. Assessment of the risk of bias in the included studies.** (A,C) Public bias assessment for in-hospital mortality. (B,D) Public bias assessment for invasive mechanical ventilation.

## 5. Conclusions

The present study increases the awareness of the potential risk of mortality after intravenous morphine treatment in patients with AHF. Owing to the increased risk, routine use of morphine in AHF patients should involve a thoughtful discussion.

## Author contributions

YWL, QLC and SHD designed, collected, analyzed and wrote this manuscript. JY, YC, HDL, SHD and XLP assisted in the conduct of study. QLC, and SHD was the principal investigator. JY, YC, HDL and XLP revised critically the paper and interpreted the data based on the study aims and statistical analysis. All authors read and approved this article for publication.

## Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shenzhen People's Hospital (SZLY2020034).

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## Conflict of interest

The authors declare no conflict of interest.

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