Impact of morphine use in acute cardiogenic pulmonary oedema on mortality outcomes

A systematic review and Meta-analysis

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Running head: Use of morphine in acute cardiogenic pulmonary oedema

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Abstract

Background: Morphine is commonly used in the management of acute cardiogenic pulmonary oedema. The European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) do not recommend the routine use of opioids in Acute Heart Failure (AHF) due to dose dependent side-effects. However, the effect morphine has remains unclear. Our study aims to investigate the link between morphine use in acute cardiogenic pulmonary oedema and mortality.

Methods: Pubmed and Embase databases were searched from inception to October 2021. All studies were included (randomised, non-randomised, observational, prospective and retrospective). The references for all the articles were reviewed for potential articles of interest with no language restrictions. Studies looking at in-hospital mortality along with other outcomes were chosen. The Newcastle-Ottawa scale was used to appraise the studies. Heterogeneity was assessed using I^2. Meta- analysis was conducted using the Review Manager Software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), by computing odds ratios (OR) for pooled in-hospital mortality and clinical outcomes

Results: Six observational studies out of the 73 publications identified were eligible for the meta-analysis giving a total sample size of 152,859 (mean age 75, males 48%). Of these, 4 were retrospective analyses. The use of morphine in acute cardiogenic pulmonary oedema was associated with an increased rate of in-hospital mortality (OR 2.39, CI 1.13 to 5.08, p=0.02), increased need for invasive ventilation (OR 6.14, CI 5.84 to 6.46, p<0.00001), increased need for non-invasive ventilation (OR 1.85, CI 1.45 to 2.36, p<0.00001), and increased need for vasopressors/inotropes (OR 2.93, CI 2.20 to 3.89, p<0.00001).

Conclusions: Based on the observational studies, morphine use in acute cardiogenic pulmonary oedema is associated with worse outcomes. Further randomised controlled trials are needed to confirm any causative effect of morphine on mortality rates in acute cardiogenic pulmonary oedema.

Keywords

Morphine; Pulmonary Oedema; Hospital Mortality; Morphine

Introduction

Morphine is one of the commonly used drugs in the management of acute cardiogenic pulmonary oedema [1]. It is recommended as a level IIb intervention under the European Society of Cardiology (ESC) guidelines to relieve dyspnoea and anxiety in the early stages of acute heart failure (AHF)[1] . Morphine helps in pulmonary oedema by reducing the preload and therefore reducing the pulmonary capillary pressure. It also reduces the afterload to a lesser extent [2]. At a cellular level, morphine and its metabolite morphine-6-glucuronide act as agonists on the mu and kappa opioid receptors [3]. The cation on mu receptors is thought to be associated with the side effects such as modification of the respiratory system and addiction [3]. Both ESC and NICE recommends not to use opioids routinely in AHF due to dose-dependent side-effects such as nausea, bradycardia, hypotension and respiratory depression [1,4]. However, prognostic benefits of morphine remain unclear; whether it simply relieves acute symptoms or if it might even worsen outcomes. There is conflicting evidence regarding potentially elevated mortality risk in AHF patients receiving morphine [5,6]. Therefore, this systematic review was conducted to find out if there is a link between morphine use in acute cardiogenic pulmonary oedema and adverse patient outcomes and to provide up-to-date evidence, identified in a systematic approach building on existing meta-analyses[7–9].

Methods

The systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary material, Table 2)[10].

Search strategy

An extensive search was carried out on PubMed and Embase databases from inception to October 2021 using key search terms such as “pulmonary oedema” OR “pulmonary edema” OR “Acute heart failure” AND “Morphine” AND “Mortality”. Mortality was our primary outcome measure. A snowballing method was used to the references of trials to broaden the search. No language or study design restrictions were applied.

Eligibility criteria

All studies (e.g. randomised, non-randomised, observational, prospective and retrospective) that reported the effects of morphine use in acute cardiogenic pulmonary oedema in adults (age >18) were included. Conference abstracts were excluded as there was inadequate detail for quality assessment. The primary outcome was in-hospital mortality.

Data analysis

All studies identified in the search were screened by two authors (T.W and R.B) individually using titles and the abstracts. Disagreements were adjudicated by a third author (V.V). Any trial with the potential of fulfilling our inclusion criteria underwent full-text evaluation. From each trial included in the systematic review, following data was extracted: study design, sample size, average age, percentage of males, presence of comorbidities such as ischaemic heart disease, hypertension, diabetes mellitus, chronic lung disorders, atrial fibrillation, serum sodium levels, serum haemoglobin (Hb) levels, serum brain natriuretic peptide levels, ejection fraction, number of participants who received morphine and number of participants in the control group.

Meta- analysis was conducted using the Review Manager Software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), by computing odds ratios (OR) for pooled in-hospital mortality and clinical outcomes. We prospectively decided to use a random effect model. Heterogeneity was assessed using the I^2. In terms of the quality of the studies we hypothesised that according to the methodological quality of the studies, the effect size may vary. To find out if any one study carried significant weight, we conducted the analysis by excluding one study at a time. Newcastle-Ottawa Scale was used to appraise the studies.

Results

A total of 106 publications were identified from database search (Figure 1 [18]). After de-duplication of 33 studies, 73 studies underwent screening. Some 67 further studies were excluded. In total, six studies were used in the meta-analysis.

This systematic review meta-analysis consists of a total sample size of 152,859 participants with a mean age 75 years, males 48%, IHD 2%, diabetes 44%, chronic lung conditions 31%, AF 31%. The characteristics of the six studies are shown in table 1.

Patient demographics including presence of comorbidities (Table 2) were similar in the patient samples who received morphine (intervention) compared to those who did not (control) across all studies. For the Dominguez-Rodriguez A[11] and Fiutowski M[12] studies, the demographics of intervention and control groups were not reported.

All six studies examined the relationship between morphine use in acute cardiogenic pulmonary oedema and in-hospital mortality. Our meta-analysis showed that morphine use in acute cardiogenic pulmonary oedema is associated with a significant 2.39-times increase in in-hospital mortality (odds ratio [OR] 2.39, 95% confidence interval [CI] 1.13 to 5.08, p=0.02 [figure 2A]). This was also true for the sub-group analysis performed on the two studies that used propensity score matched analysis with OR 1.40, 95% CI 1.08-1.82, p=0.01 (as shown in Figure 1 in supplementary material).

Furthermore, pooled analysis of three studies [5,13,14] that examined the relationship between morphine use and the need for inotropes/vasopressors in acute cardiogenic pulmonary oedema showed almost a threefold significant increase in need for inotropes/vasopressors in the morphine group as compared with the control (Pooled OR 2.93, 95% CI 2.20 to 3.89, p<0.00001 [figure 2B]).

The association between morphine use and need for invasive ventilation was examined in three studies. Two out of these showed an increase in the need for invasive ventilation in the morphine group while one showed an increase in need in the control group (figure 2C). Our meta-analysis was carried out to reveal that overall, morphine use is associated with a 6.14 fold increase in the need for invasive ventilation compared to non-morphine use (OR 6.14, 95% CI 5.84 to 6.46, p<0.00001). Besides, two studies reported data for non-invasive ventilation. Pooled analysis demonstrated an overall increase of 1.85 times in the patients on morphine compared to controls (OR 1.85, 95% CI 1.46 to 2.36, p<0.00001[figure 2D]).

Funnel plot and sensitivity analyses were undertaken and shown in figure 3 and figure 4 respectively. The appraisal standards assessed by Newcastle Ottawa Scale is shown table 1 in supplementary material.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the trial selection process

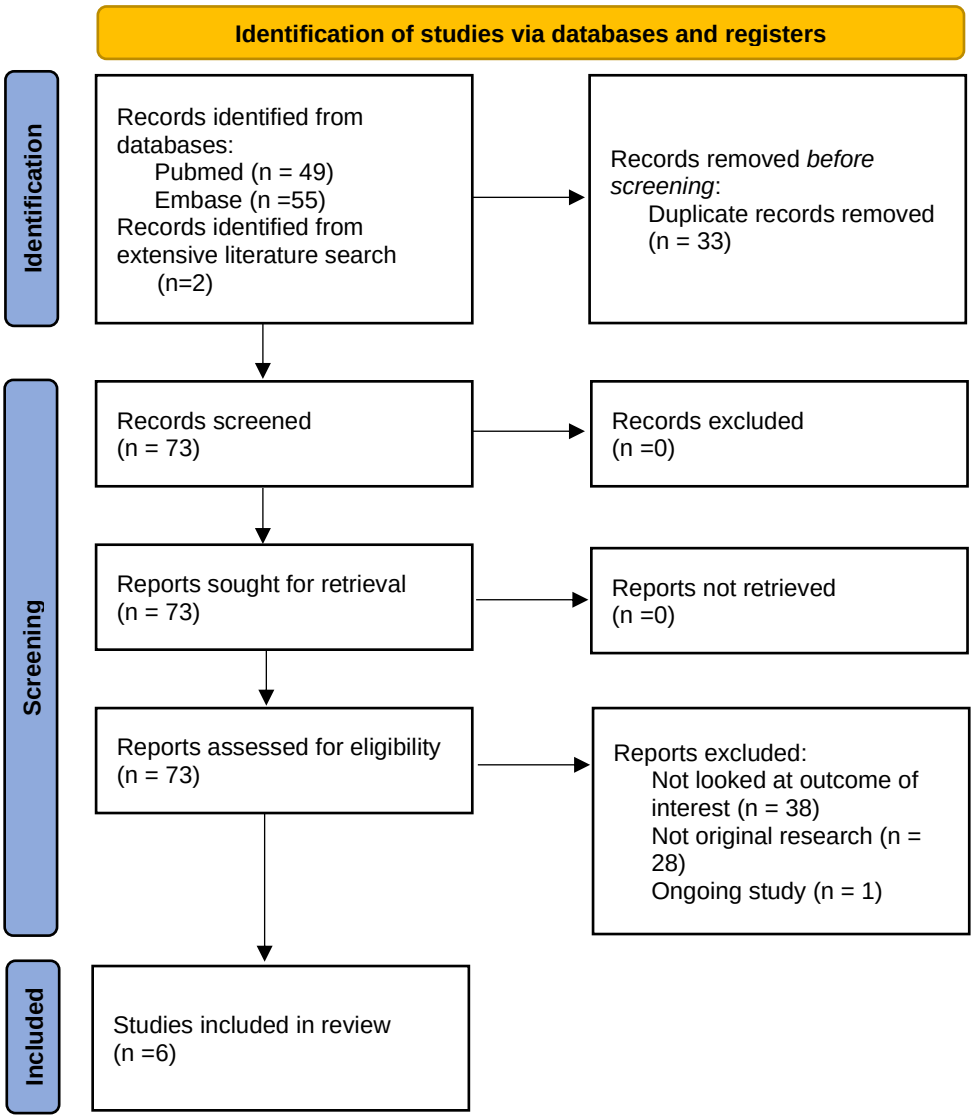


Table 1: Characteristics of the selected studies

Study Name	Study Design	Sample size n	Male %	Mean age yrs	Outcomes studied
Caspi O et al 2019	Retrospective Observational cohort	1344	41	78	Invasive ventilation In-hospital mortality Non-invasive ventilation Inotrope use Acute kidney injury
Miró Ò et al 2017	Prospective Observational Cohort	550	57	81	In hospital mortality 30-day mortality Need for inotropes/vasopressors Need for non-invasive ventilation Need for mechanical ventilation
Dominguez-Rodriguez A et al 2016	Retrospective Observational Cohort	991	28	67	In-hospital mortality
Lakobishvili et al 2011	Prospective Observational Cohort	2336	45	76	In hospital mortality Need for IV inotropes
Peacock W et al 2007	Retrospective Observational cohort	147,362	48	75	In hospital mortality Hospitalization length ICU admission ICU length of stay Mechanical ventilation

Fiutowski M et al 2004	Retrospective Observational Cohort	276	46	70	In-hospital mortality

Table 2: patient demographics; morphine group vs non morphine group. Ischaemic Heart Disease (IHD), Hypertension (HTN), Diabetes Mellitus (DM), Chronic Lung Disease CLD), Atrial Fibrillation (AF), Haemoglobin (Hb)

Demographics	Morphine group (Intervention) n = 21947 (%)	Non-morphine group (control) n = 129645 (%)
Age	73	75
Male	10286 (47)	62769 (48)
IHD	8414 (38)	44611 (34)
HTN	16540 (75)	95024 (73)
DM	9957 (45)	57272 (44)
CLD	7163 (33)	39797 (31)
AF	6171 (28)	40885 (32)
Sodium	138	139
Hb	12	12

Figure 2A: Morphine use and in-hospital mortality

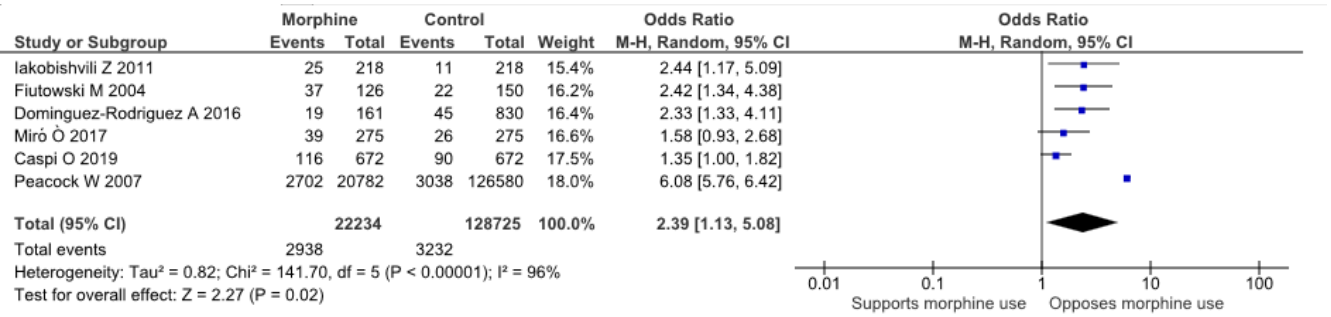


Figure 2A: Morphine use in acute cardiogenic pulmonary oedema is associated with a 2.39-times increase in in-hospital mortality (odds ratio [OR] 2.39, 95% confidence interval [CI] 1.13 to 5.08)

Figure 2B: Morphine use and need for inotropes/vasopressors

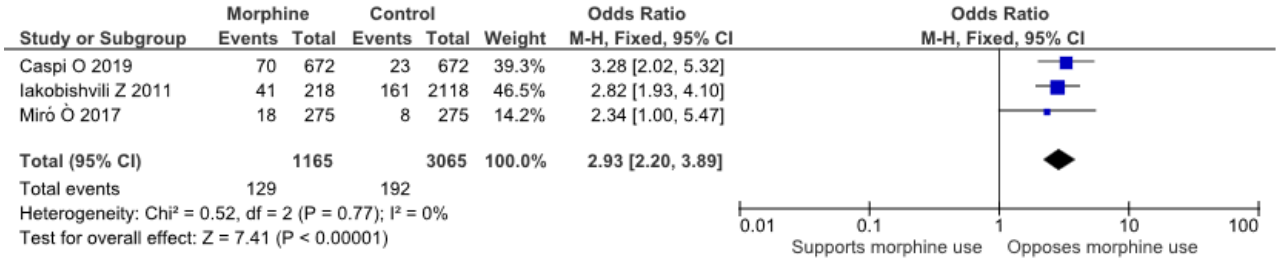


Figure 2B: Morphine use in acute cardiogenic pulmonary oedema is associated with 2.93 times increased need for inotropes/vasopressors (OR 2.93, 95% CI 2.20 to 3.89)

Figure 2C: Morphine use and need for invasive ventilation

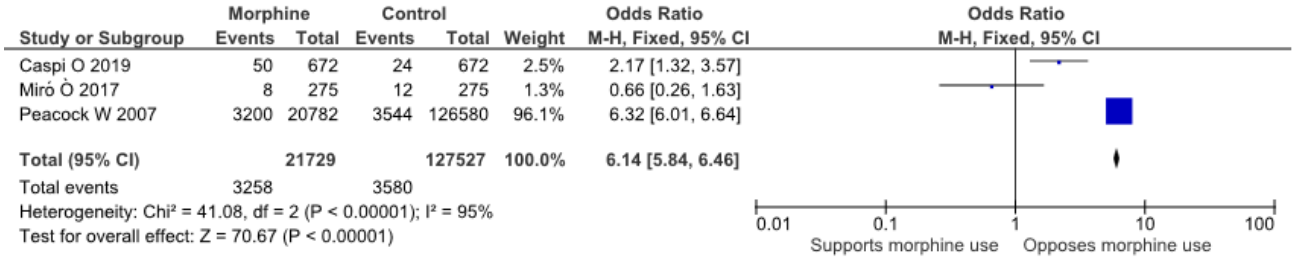


Figure 2C: Morphine use is associated with a 6.14 fold increase in the need for invasive ventilation (OR 6.14, 95% CI 5.84 to 6.46)

Figure 2D: Morphine use and need for non-invasive ventilation

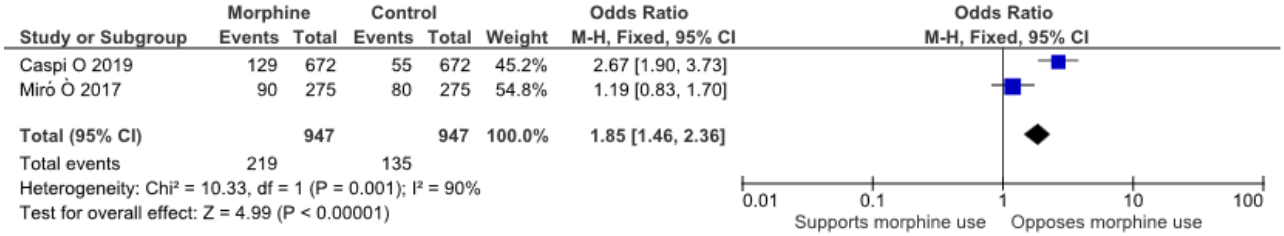


Figure 2D: Morphine use is associated with a 1.85 fold increase in the need for non-invasive ventilation (OR 1.85, 95% CI 1.46 to 2.36)

Table 3: Patient demographics.

Ischaemic Heart Disease (IHD), Hypertension (HTN), Diabetes Mellitus (DM), Chronic Lung Disease CLD), Atrial Fibrillation (AF), Haemoglobin (Hb)

Study name	year	Sample size	Mean age (yrs)	Male (%)	IHD	HTN	DM	CLD	AF
Caspi O	2019	1344	78	41	366	1013	730	189	557
Miró Ò	2017	550	81	57	202	481	266	118	231

Dominguez-Rodriguez A	2016	991	67	28	221	620	425	161	301
Iakobishvili Z	2011	2336	76	45	922	1785	1207	451	680
Peacock W	2007	147362	75	48	1,586	108,285	65,026	46,202	45,588
Fiutowski M	2004	276	70	46	262	191	97	-----	37

Figure 3: Funnel plot

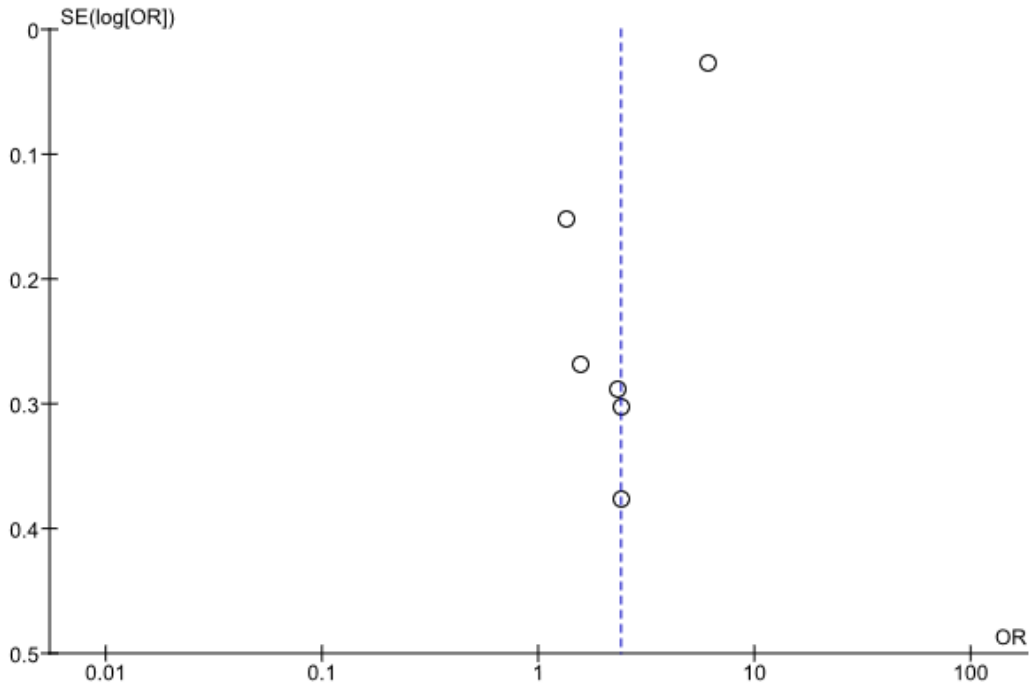


Figure 4: sensitivity analysis for in-hospital mortality

Figure 4A: sensitivity analysis with Lakobishvili Z. study excluded

Study or Subgroup	Morphine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Iakobishvili Z 2011	25	218	11	218	0.0%	2.44 [1.17, 5.09]
Fiutowski M 2004	37	126	22	150	19.2%	2.42 [1.34, 4.38]
Dominguez-Rodriguez A 2016	19	161	45	830	19.4%	2.33 [1.33, 4.11]
Miró Ò 2017	39	275	26	275	19.6%	1.58 [0.93, 2.68]
Caspi O 2019	116	672	90	672	20.7%	1.35 [1.00, 1.82]
Peacock W 2007	2702	20782	3038	126580	21.2%	6.08 [5.76, 6.42]
Total (95% CI)		**22016**		**128507**	**100.0%**	**2.38 [1.03, 5.51]**
Total events	2913		3221			

Heterogeneity: Tau² = 0.86; Chi² = 136.54, df = 4 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.03 (P = 0.04)

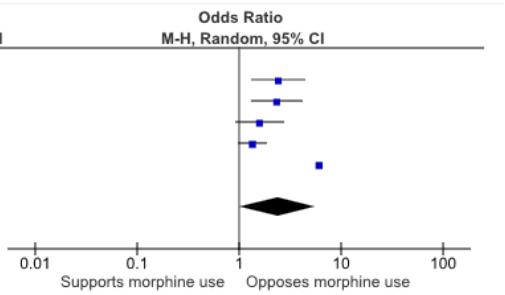


Figure 4B: sensitivity analysis with Fiutowski M. study excluded

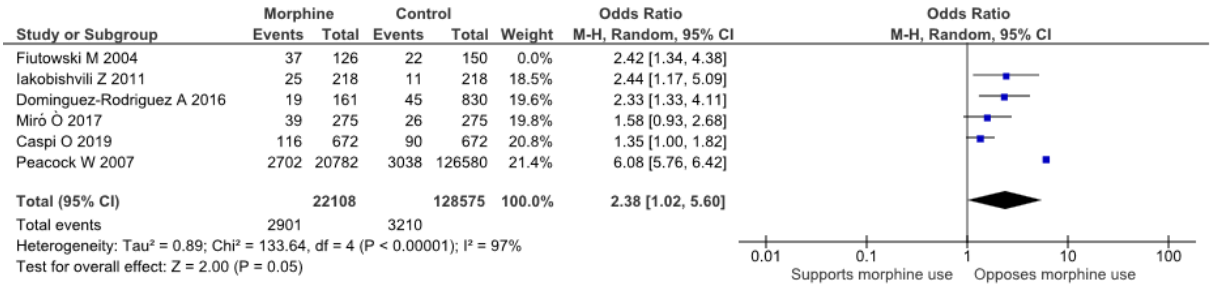


Figure 4C: sensitivity analysis with Dominguez-Rodriguez A study excluded

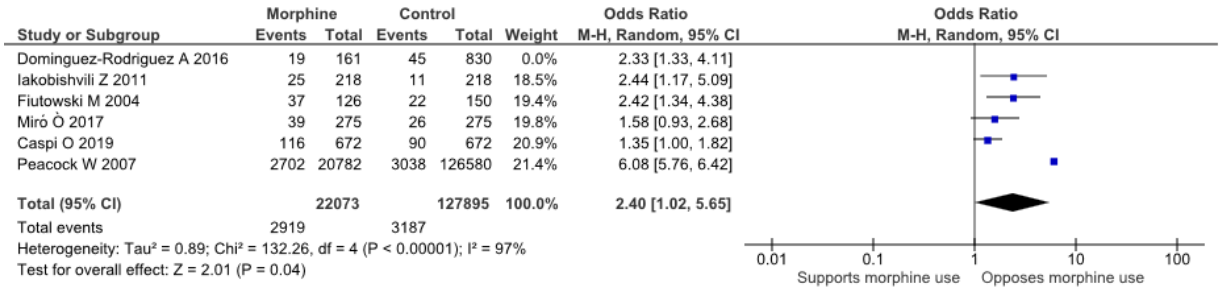


Figure 4D: sensitivity analysis with Miró Ò study excluded

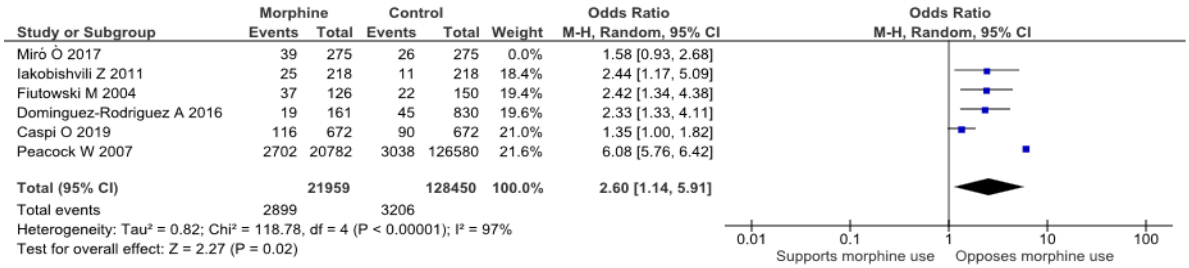


Figure 4E: sensitivity analysis with Caspi O study excluded

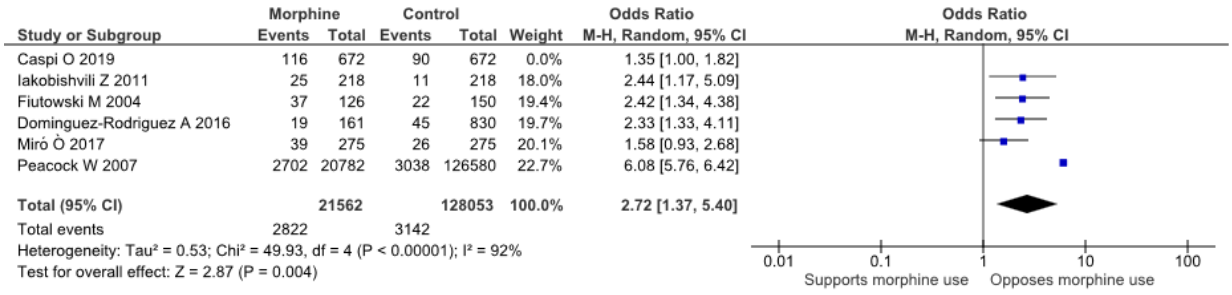
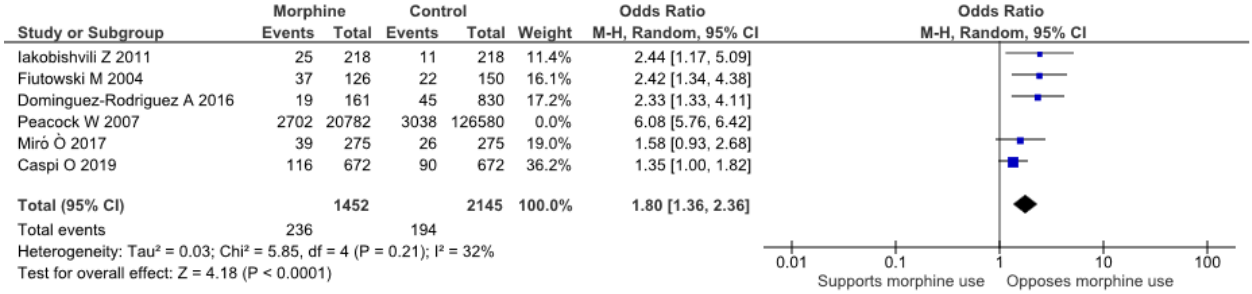


Figure 4F: sensitivity analysis with Peacock W study excluded



Discussion

Our systematic review and meta-analysis demonstrated increased in-hospital mortality with morphine use in acute cardiogenic pulmonary oedema. Morphine use is also seen to be associated with an increased need for inotropes/vasopressors, invasive ventilation and non-invasive ventilation. Overall, it is linked to significantly worsening outcomes in patients with acute cardiogenic pulmonary oedema.

None of the included studies were RCTs. So, we are unable to confirm whether the groups were similar or not. However, it is likely that the groups of patients who received morphine were more unwell with limitation of therapeutic effort. This could well have been a confounder as the studies were observational. Lack of randomised controlled trials can be explained by the fact that morphine use is usually associated with use in severely unwell patients and therefore randomised or placebo-controlled trials around its usage is rarely approved. However, propensity score matched analysis provides insight into these scenarios where higher levels of evidence are lacking. In our meta-analysis, two of the primary researches are propensity score matched analyses. The meta-analyses of these studies on in hospital mortality also showed adverse outcomes with morphine use (OR 1.40, 95% CI 1.08-1.82, p=0.01) as shown in Figure 1 in supplementary material.

Currently, evidence supporting the use of morphine in this patient group is not available. Hence, current practise uses a therapeutic approach where a potentially harmful class of drugs is used in these acutely ill patients[15]. The European Society of Cardiology suggests cautious use of morphine in patients with severe dyspnoea, mainly in those with acute pulmonary oedema. Similarly, the American Heart Association/American College of Cardiology recommends the use of morphine therapy only in palliative care of end-stage heart failure[16]. Evidence for the use of morphine in acute cardiogenic pulmonary oedema in the form of large randomised controlled trials is lacking[15].

The use of morphine in dyspnoea and anxiety is well known[17]. In acute cardiogenic pulmonary oedema, there is increased vascular resistance due to release of endogenous catecholamines[15]. Morphine with its

vasodilatory properties results in decreased venous tone which reduces vascular return to the right heart and eventually a reduced right ventricular output [14]. This allows the weaker left ventricle to function at a lower filling pressure. This will also cause hypotension and a decrease in cardiac output. The decrease in cardiac output is perhaps related to an increased need for ICU admissions and endotracheal intubations[18].

Our meta-analysis revealed an increase need for both invasive and non-invasive ventilation. The beneficial effect of morphine use in acute cardiogenic pulmonary oedema seems to be the anxiolytic effect and the systemic vascular resistance. However, it may be possible that alternative therapy, such as benzodiazepines for anxiety, to provide similar effects without the increased adverse effects seen in morphine[18]. Further research will of course be needed to test the efficacy and safety of these therapies in acute heart failure.

The detrimental effects of morphine can also be partially explained by its interactions with other medications. Morphine when combined with antiplatelets such as ticagrelor, clopidogrel prasugrel demonstrated a delayed activity. Besides, there is evidence of a decreased heart rate and consequently cardiac output with morphine[19]. This can potentially decrease myocardial perfusion and lead to ischaemia and cardiogenic shock. These cardiac effects may be fatal in patients with ischaemic heart disease who are already at risk of heart failure[19].

The effects of morphine remain controversial. Midazolam vs Morphine in Acute Pulmonary Oedema (MIMO) trial, a multi-centre prospective randomised study that aims to assess the safety of morphine in acute cardiogenic pulmonary oedema will address the gaps in our knowledge in the field[20]. It is important to note that this RCT does not have a control group, as it is unethical not to provide symptomatic relief in these patients.

Study limitations

Five out of the six studies used in our meta-analysis are retrospective studies. Only observational studies are available. Due to the lack of evidence from randomised controlled trials, it is difficult to prove causality. Nevertheless, this study shows a significant association between morphine use and mortality. Therefore, it essentially allows us to risk-stratify the patients who receive morphine (at the discretion of the clinical team) and identify these patients as "high risk" and therefore provide increased vigilance and therapy. Furthermore, the total dose of morphine used and the timings of administration in the patients were not given in the studies making it impossible to find out if outcomes were affected by dose differences. As such, we used a binary measure of any morphine or no morphine used. In addition, it was not possible to identify whether the causes of in-hospital mortality in the participants were of a cardiac origin or not. Nevertheless, evidence suggests that most patients admitted with acute pulmonary oedema die from heart failure related causes[21], so a cardiac-related death is more likely.

Conclusions

In-hospital mortality along with the use of inotropes, invasive and non-invasive ventilation were higher in patients with acute cardiogenic pulmonary oedema who received morphine, compared to those who did not. However, due to lack of evidence from randomised controlled trials, a causative effect could not be investigated. Hence, until randomised data is available our study supports the current guidelines in suggesting cautious use of morphine in the management of acute cardiogenic pulmonary oedema.

Declarations

Funding

Not applicable

Conflict of interest/competing interests

No conflict of interest or competing interests to declare.

Availability of data and material

The authors confirm that this manuscript is an honest, transparent and accurate reflection of the study. No aspect of the study deemed important is omitted.

Code availability

Review Manager software version 5.3 was used for deriving the forest plots, sensitivity analyses and funnel plot.

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Supplementary material

Table 1: quality appraisal, Newcastle-Ottowa Scale

Study	Selection				Comparability	Outcome			Overall quality
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort from the same source as exposed**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of design or analysis**	**Assessment of outcome**	**Was follow up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	
Caspi O et al 2019	Participants were truly representative of adults in Haifa Israel with a diagnosis of HF	Yes	Morphine administered in hospital	Yes	Propensity score matching analysis used	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Good
Miró Ò et al 2017	Participants were truly representative of adults with HF in as it a multicentre study covering 34 Spanish EDs	Yes	Morphine administered in hospital	Yes	Propensity score matching analysis used	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Good
Dominguez-Rodriguez A et al 2016	Participants were truly representative of adults with HF presenting to a Spanish ED	Yes	Morphine administered in hospital	Yes	Adjusted for variables	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Good

Lakobishvili et al 2011	Participants were truly representative of adults with HF in Israel as data were based on a nationwide survey	yes	Morphine administered in hospital	Yes	Propensity score matching analysis used – only raw data available for meta-analysis	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Good
Peacock W et al 2007	Participants were truly representative of adults with HF in America as the data are based on a national study	Yes	Morphine administered in hospital	Yes	Comparison risk adjusted for indices known to affect the outcome of interest	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Good
Fiutowski M et al 2004	Participants were truly representative of adults with HF in Lodz city in Poland	Yes	Morphine administered in hospital	Yes	No evidence of controlling for confounders	Outcome was in hospital mortality	Yes	Looked at in hospital mortality during the same admission	Poor

Table 2: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4

Section and Topic	Item #	Checklist item	Location where item is reported
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	N/A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in	P7

Section and Topic	Item #	Checklist item	Location where item is reported
		the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp. Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Fig 4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supp. Table 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supp. Table 1
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P16
	23b	Discuss any limitations of the evidence included in the review.	P16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P19
Competing interests	26	Declare any competing interests of review authors.	P19
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

Figure 1: Morphine use and in-hospital mortality for studies with propensity score matched analysis