

Correlations between Morphine Use and Adverse Outcomes in Acute ST-Segment Elevation Myocardial Infarction with Acute Heart Failure: a retrospective study

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Abstract

Background: Studies examining the safety of intravenous morphine use for acute heart failure (AHF) have reported inconsistent results.

Objective: The comprehensive meta-analysis assessed and compared the clinical outcomes of intravenous morphine use in AHF.

Methods: We formally searched electronic databases before June 2020 to identify potential studies. All clinical trials were eligible for inclusion if they compared intravenous morphine or not in patients with AHF.

Results: 3 propensity-matched cohorts and 2 retrospective analysis with a total of 151867 patients met the inclusion criteria were included in our meta-analysis (intravenous morphine group=22072, without morphine group=127895). The use of intravenous morphine was associated with increased risk of in-hospital mortality [over all odds ratio (OR)=5.49, 95% confidence interval (CI) 5.20 to 5.79, $p<0.001$, $I^2=96.7\%$; subgroup analysis: OR=1.60, 95%CI 1.27-2.02, $I^2=0\%$; OR=1.53, 95%CI 1.20-1.96, $I^2=7\%$] and invasive mechanical ventilation (OR=6.08, 95% CI 5.79 to 6.40, $p<0.001$, $I^2=94.2\%$; subgroup analysis: OR=1.74, 95%CI 1.21-2.49, $I^2=62.3\%$). However, there was no significant association of longtime time mortality with intravenous morphine (Hazards ratio =1.17; 95% CI 0.99–1.36, $p=0.14$; I^2 32%).

Conclusion: In AHF patients, intravenous morphine administration for relieving dyspnea was associated with in-hospital mortality and invasive mechanical ventilation, but not for longtime mortality.

Background

Morphine has been recommended for treatment of chest pain during acute myocardial infarction (AMI)[1-2] and the amelioration of pulmonary edema in acute heart failure (AHF) for several decades[3]. However, intravenous morphine has been shown to cause slower absorption, delayed onset of action, and reduced bioavailability of oral anti-platelet agents, which may lead to failure of early anti-platelet treatment in susceptible individual patients[3-4]. Moreover, intravenous morphine can cause brainstem respiratory center suppression, heart rate depression, and hypotension in patients with heart failure[5]. Despite its longstanding use in AMI and AHF patients, a consensus on the safety of intravenous morphine in these patients has yet to be reached, with different published studies reporting conflicting results.

The French Registry of Acute STEMI (FAST-MI) study included 2438 ST-elevation MI (STEMI) patients, of whom 453 patients received morphine and 1985 patients did not, and found that mortality and complications among STEMI patients while receiving in-hospital treatment or during 1 year of follow-up were not associated with morphine use[6]. An important limitation of that study was that only 6% of the cases treated with morphine were Killip class ≥ 2 in the FAST-MI study. In another study with a higher proportion of patients with Killip class ≥ 2 of 14.8% (88/617), morphine use correlated with higher death or recurrent MI with 30 days of follow-up in patients with non-ST-segment elevation acute coronary

syndrome (NSTEMI-ACS)[7]. Moreover, in the multivariate analysis of Zaza et al., morphine use was associated with a high in-hospital and 30-day mortality rate [odds ratio (OR)=2.0, 1.1–3.5, p=0.02] and was most strongly associated with admission Killip class III–IV in patients with or without ACS (OR=2.3, 1.5–3.5)[8].

At present, the available data regarding the safety of morphine use in cases of STEMI with AHF (Killip ≥ 2) remain insufficient.

Methods

Study Design

From January 2017 to December 2019, 275 STEMI with AHF patients undergoing primary percutaneous coronary intervention (PPCI) were consecutively enrolled and separated into two groups: patients who received morphine (n=125) and patients who did not receive morphine (n=150). The combined endpoints were the incidences of major adverse cardiovascular events (MACEs) and the requirement of invasive mechanical ventilation while receiving in-hospital treatment and during hospitalization and 1 year of follow-up. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Hospital.

Inclusion Criteria

Eligible patients with STEMI and a Killip class II–IV at admission were included. All the included patients had been sent to the hospital within 12 hours from the onset of acute chest pain and were immediately scheduled to receive PPCI. The diagnosis of STEMI was made according to the 2017 Guidelines for STEMI, including ST-segment elevation ≥ 0.2 – 0.3 mV in two contiguous leads[1]. Intravenous morphine was administered at dosage from 3 mg to 6 mg with the first 24 h after hospital admission.

Exclusion Criteria

Patients who received treatment with morphine before hospital admission or beyond 24 h after admission were excluded from participation in the preset study. In addition, patients with Killip class I at admission, age >90 years, a coexisting major hemorrhage, or a large cerebral infarction at admission also were excluded.

Study Endpoints

The primary endpoint was in-hospital complications including a composite of MACEs (Cardiac death + recurrent MI + unstable angina + cardiogenic shock), cardiac death, recurrent MI, unstable angina, and cardiogenic shock[9]. The secondary endpoint was the requirement of in-hospital invasive mechanical ventilation. Finally, the incidence rates of cardiac death, all-cause death, and MACEs over 1 year of follow-up were evaluated. Follow-up data were collected by telephone interview.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Data are reported as mean \pm standard deviation or count (percentage). Group comparisons of continuous data were conducted using Student's test or Kruskal-Wallis test, whereas group comparisons of categorical data were performed using the Chi-squared or Fisher Exact test. Univariable (binary logistic regression) and multivariable analysis was applied to evaluate the adjusted odds ratios (ORs) for the association of morphine with different outcomes. MACE-free survival, all-cause death, and cardiac death were analyzed by the Kaplan–Meier method (log rank test). Statistical significance was defined by a p value <0.05 .

Results

Baseline Characteristics of STEMI Patients with AHF

Morphine was given in 125 (45.45%) patients in this study. The baseline demographic features, angiographic characteristics, and treatment details are presented in Table 1. The mean ages of the patients in the with morphine and without morphine groups were 61.70 ± 13.67 years and 58.71 ± 13.03 years, respectively ($p=0.066$). Additionally, no statistically significant differences were found between the two groups for the percentage of males, body mass index (BMI), systolic blood pressure (SBP), heart rate (HR), coronary risk factors, chronic obstructive pulmonary disease (COPD), clinical manifestations, Killip class at admission, symptom onset to first medical contact, angiographic characteristics, final flow of thrombolysis in myocardial infarction (TIMI), or medical treatment. However, non-significant trends were observed for increasing age and a higher percentage of Killip IV patients among those who received morphine treatment at baseline.

Primary and Secondary Endpoints In-hospital

The occurrence rates of MACEs in the morphine and without morphine groups were 39.20% and 26.67%, respectively ($p=0.037$; Table 2). The group of patients treated with morphine had higher frequencies of in-hospital cardiac death (15.2% vs 6.67%, $OR=2.509$, $p=0.035$) and cardiogenic shock (14.40% vs 6.00%, $OR=2.636$, $p=0.033$; Figure 1). No differences in the frequencies of recurrent MI (16.00% vs 12.00%, $p=0.434$) or unstable angina (13.60% vs 9.33%, $p=0.287$) were observed between the groups. However, the percentage of patients who required invasive mechanical ventilation (secondary endpoint) was higher in the morphine group than in the without morphine group (19.20% vs 10.67%, respectively, $p=0.031$, $OR=2.308$; Table 2).

Survival of STEMI Patients with AHF During 1 Year of Follow-up after PPCI

The Kaplan-Meier survival-free curves for MACEs in patients in the with morphine and without morphine groups showed no differences (Log-rank test, $p=0.436$; Figure 3). Additionally, no significant difference in survival free of cardiac death or all-cause death was observed between the groups throughout the follow-up period (log-rank test, $p=0.392$ and $p=0.265$, respectively; Figure 2).

Discussion

We performed the first retrospective cohort study to evaluate the safety of morphine use in patients with STEMI and AHF undergoing PPCI. The main findings of the study confirmed that morphine use significantly increased the composite frequency of primary outcomes (cardiovascular death and cardiogenic shock) as well as the requirement for invasive mechanical ventilation in-hospital. In contrast, no such association with adverse outcomes was observed after 1 year of follow-up.

The guidelines for the management of AMI in patients with STEMI continue to recommend intravenous morphine as a drug of choice for the alleviation of chest pain, with a class IIA indication[10]. Morphine administration is expected to reduce sympathetic tone and decrease venous return, which leads to increased cardiac workload[11] and results in smaller infarcts and significantly less microvascular obstruction determined by cardiac magnetic resonance[12]. Nevertheless, studies have revealed a correlation between morphine use and worse mortality. In 2005, the observational CRUSADE registry study was the first to demonstrate that intravenous morphine administration in patients presenting with NSTEMI-ACS was statistically associated with a higher rate of adverse outcomes (3.80% vs 3.00% for MI, 3.80% vs 2.30% for cardiogenic shock, 5.50% vs 4.70% for in-hospital death, and 8.50% vs 7.10% for composite of death and MI)[13]. Zaza et al. found that intravenous morphine was associated with in-hospital MACEs and 30-day mortality and most strongly associated with admission Killip class III–IV (OR=2.3, 1.5–3.5)[9]. According to the studies described above, morphine was not associated with significant adverse outcomes in AMI without HF, but the opposite result was observed in AMI patients with HF.

In our study, we included STEMI patients with advanced Killip class II–IV at admission, which was different from previous studies. Administration of intravenous morphine was associated with elevated risks of cardiac death (OR=2.509), cardiogenic shock (OR=2.636), and a need for mechanical ventilation (OR=2.308) during in-hospital treatment for STEMI with AHF. Similar results were unequivocally confirmed by the observational ADHERE (acute decompensated heart failure national registry) analysis, which revealed that intravenous morphine was independently related with an increased rate of adverse events, including a greater frequency of mechanical ventilation (15.40% vs 2.80%, $p<0.001$), prolonged hospitalization (5.60 vs 4.20 days, $p<0.001$), more ICU admissions (38.70% vs 14.40%, $p<0.001$), and higher mortality (13.00% vs 2.40%, $p<0.001$) in acute decompensated heart failure[5]. Caspi et al. demonstrated a strong relationship between morphine dosage and in-hospital mortality (17.4% vs 13.4%, OR=1.43). Additionally, intravenous morphine use significantly contributed to a marked risk for the need for additional mechanical ventilation (7.4% vs 3.6%, OR=2.13)[14]. The following factors may explain these results. First, intravenous morphine use might induce respiratory depression and increase the rate of intubation[5]. Second, morphine inhibits gastrointestinal absorption and decreases peak plasma levels of oral antiplatelet drug, potentially leading to decreased treatment efficacy[15–17]. From IMPRESSION trial, co-administration of morphine and ticagrelor resulted in a weaker and retarded antiplatelet effect in patients with AMI[15]. However, an administration of GP IIb/IIIa would diminish the negative impact of morphine on oral P2Y₁₂ receptor, which just 71.2% of patients received GP IIb/IIIa treatment in the iv

morphine group v.s 83.3% of patients received GP IIb/IIIa treatment in the without morphine group ($p=0.096$) in our study. Accordingly, recurrent MI and unstable angina in-hospital in the iv morphine group was higher but did not reach statistical significantly in this study. Furthermore, intravenous morphine use has been linked to multiple gastrointestinal dysfunction, including inhibition of gut motility and vomiting, which significantly affects antiplatelet drug absorption and the occurrence of aspiration pneumonia[18].

Our data also showed that morphine use was not associated with long-time adverse outcomes over 1-year follow-up. Our result was similar to that reported by Zaza[8]. The perhaps reason was that the short-time use of iv morphine was significantly associated with high requirement of in-hospital invasive mechanical ventilation, but not increase recurrent MI and unstable angina in-hospital or during follow-up in STEMI with AHF.

We should acknowledge the limitations of the present study. First, the most obvious limitation of the cohort trial is the non-randomized, retrospective nature. Accordingly, there was a non-significant trend toward older age and a higher percentage of Killip IV cases among patients receiving morphine at baseline. Other unmeasured confounding factors including that decisions with respect to morphine use differed between operators. Secondly, a subgroup study considering different Killip classes should be completed to confirm the different clinical results with morphine use. Additionally, we did not record the dosage of intravenous morphine administered to the morphine group. A previous study demonstrated a dose-dependent risk of morphine in terms of the risk of needing invasive ventilation and the risk of mortality[8]. Finally, larger multicenter, randomized controlled trials are needed to provide more convincing data.

Conclusion

In conclusion, the results of this study indicate that increased awareness of the potential adverse clinical effects, including cardiac mortality and invasive mechanical ventilation, of in-hospital intravenous morphine use is warranted in STEMI patients with AHF.

Declarations

Acknowledgements

No

Author Contributions: Yaowang Lin collected, analyzed and wrote this manuscript. JieYuan, Huadong Liu, Yong Zhu and Xinli Pang assisted in the conduct of study. Shaohong Dong was the principal investigator.

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Availability of data and materials

The datasets are de-identified and available from the first-author or corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of the Hospital. All participants provided written informed consent.

Consent for publication

Not applicable

Conflicts of interest

No conflict of interest

References

1. Arslan F, Bongartz L, Ten Berg JM, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: comments from the Dutch ACS working group. *Neth Heart J*. 2018; **26**(9): 417-21.
2. Timmis AD, Rothman MT, Henderson MA, Geal PW, Chamberlain DA. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *Br Med J*. 1980; **280**(6219): 980-2.
3. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2015; **8**(1).
4. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2014; **63**(7): 630-5.
5. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J*. 2008; **25**(4): 205-9.
6. Puymirat E, Lamhaut L, Bonnet N, et al. Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI programme. *Eur Heart J*. 2016; **37**(13): 1063-71.
7. Furtado RHM, Nicolau JC, Guo J, et al. Morphine and Cardiovascular Outcomes Among Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Undergoing Coronary Angiography. *J Am Coll Cardiol*. 2020; **75**(3): 289-300.
8. Iakobishvili Z, Cohen E, Garty M, et al. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. *Acute Card Care*. 2011; **13**(2): 76-80.

9. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv.* 2019; **94**(1): 29-37.
10. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018; **39**(2): 119-77.
11. Chen A, Shariati F, Chan T, Lebowitz D. A Review of Adverse Outcomes Following Intravenous Morphine Usage for Pain Relief in Acute Coronary Syndrome. *Cureus.* 2018; **10**(9): e3246.
12. Eitel I, Wang J, Stiermaier T, et al. Impact of Morphine Treatment on Infarct Size and Reperfusion Injury in Acute Reperfused ST-Elevation Myocardial Infarction. *J Clin Med.* 2020; **9**(3).
13. Gross GJ, Gross ER, Peart JN. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CR USADE Quality Improvement Initiative. *Am Heart J.* 2005; **150**(6): e3.
14. Caspi O, Naami R, Halfin E, Aronson D. Adverse dose-dependent effects of morphine therapy in acute heart failure. *Int J Cardiol.* 2019.
15. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J.* 2016; **37**(3): 245-52.
16. Thomas MR, Morton AC, Hossain R, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb Haemost.* 2016; **116**(1): 96-102.
17. Lapostolle F, Van't Hof AW, Hamm CW, et al. Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine. *Am J Cardiovasc Drugs.* 2019; **19**(2): 173-83.
18. Gil V, Dominguez-Rodriguez A, Masip J, Peacock WF, Miro. Morphine Use in the Treatment of Acute Cardiogenic Pulmonary Edema and Its Effects on Patient Outcome : A Systematic Review. *Curr Heart Fail Rep.* 2019; **16**(4): 81-8.

Tables

Table 1. Baseline characteristics of the included STEMI with AHF patients according to treatment group.

Characteristics	with morphine group N = 125	without morphine group N = 150	p
Total			
Age (years)	61.70 ± 13.67	58.71 ± 13.03	0.066
Male, n (%)	99 (79.2)	126 (84.0)	0.319
Body mass index, kg/m ²	24.42 ± 3.29	24.50 ± 5.035	0.861
SBP (mmHg)	134.94 ± 23.86	138.34 ± 24.59	0.250
HR (bpm)	81.56 ± 16.21	79.16 ± 19.18	0.271
Hypertension, n (%)	51 (40.8)	78 (52.0)	0.074
Diabetes mellitus, n (%)	31 (24.8)	28 (18.7)	0.290
Current smoking, n (%)	69 (55.2)	79 (52.7)	0.811
COPD, n (%)	8 (6.4)	9 (6.0)	0.909
Previous MI, n (%)	6 (4.8)	9 (6.0)	0.792
Previous PCI, n (%)	4 (3.2)	6 (4.0)	0.968
Symptom onset to first medical contact (h)	9.45	8.49	0.241
Killip class at admission			
Class II-III	109 (87.2)	137 (91.3)	0.451
Class IV	16 (12.8)	13 (8.7)	0.534
Angiographic characteristics			
LM, n (%)	5 (4.0)	6 (4.0)	0.757
Single vessel	47 (37.6)	51 (34.0)	0.621
Multivessel, n (%)	74 (59.2)	95 (63.3)	0.564
Stent, n (%)	122 (97.6)	149 (99.3)	0.334
Final Flow TIMI ≥2, n (%)	120 (96.0)	146 (97.3)	0.736
Medical treatment			
Aspirin, n (%)	125 (100.0)	150 (100.0)	—
Clopidogrel, n (%)	14 (11.2)	11 (7.3)	0.139
Ticagrelor, n (%)	111 (88.8)	139 (92.7)	0.299
GP IIb/IIIa	90 (71.2)	125 (83.3)	0.096
Statin, n (%)	125 (100.0)	150 (100.0)	—
ACEI/ARB, n (%)	103 (82.4)	132 (88.0)	0.158
Beta-blocker, n (%)	117 (93.6)	135 (90.0)	0.276
eGFR, ml/(min.1.73 m ²)	77.37 ± 24.95	80.75 ± 23.86	0.256
LVEF, %	49.74 ± 10.75	49.39 ± 9.66	0.774
Median length of hospital stay (days)	6.88 ± 2.80	6.13 ± 2.17	0.836

SBP = systolic blood pressure; HR = heart rate; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; LM = left main; TIMI = thrombolysis in myocardial infarction; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction.

Table 2. Primary and secondary outcomes in-hospital for patients in the two groups.

	With morphine group (n=125)	Without morphine group (n=150)	p
MACE, n (%)	49 (39.20%)	40 (26.67%)	<i>0.037</i>
Cardiac death	19 (15.2%)	10 (6.67%)	<i>0.035</i>
Recurrent MI	20 (16.00%)	18 (12.00%)	0.434
Unstable angina	17 (13.60%)	14 (9.33%)	0.287
Cardiogenic shock	18 (14.40%)	9 (6.00%)	<i>0.033</i>
Invasive mechanical ventilation, n (%)	24 (19.20%)	16 (10.67%)	<i>0.031</i>

MACE = major adverse cardiac event; MI = myocardial infarction.

Figures

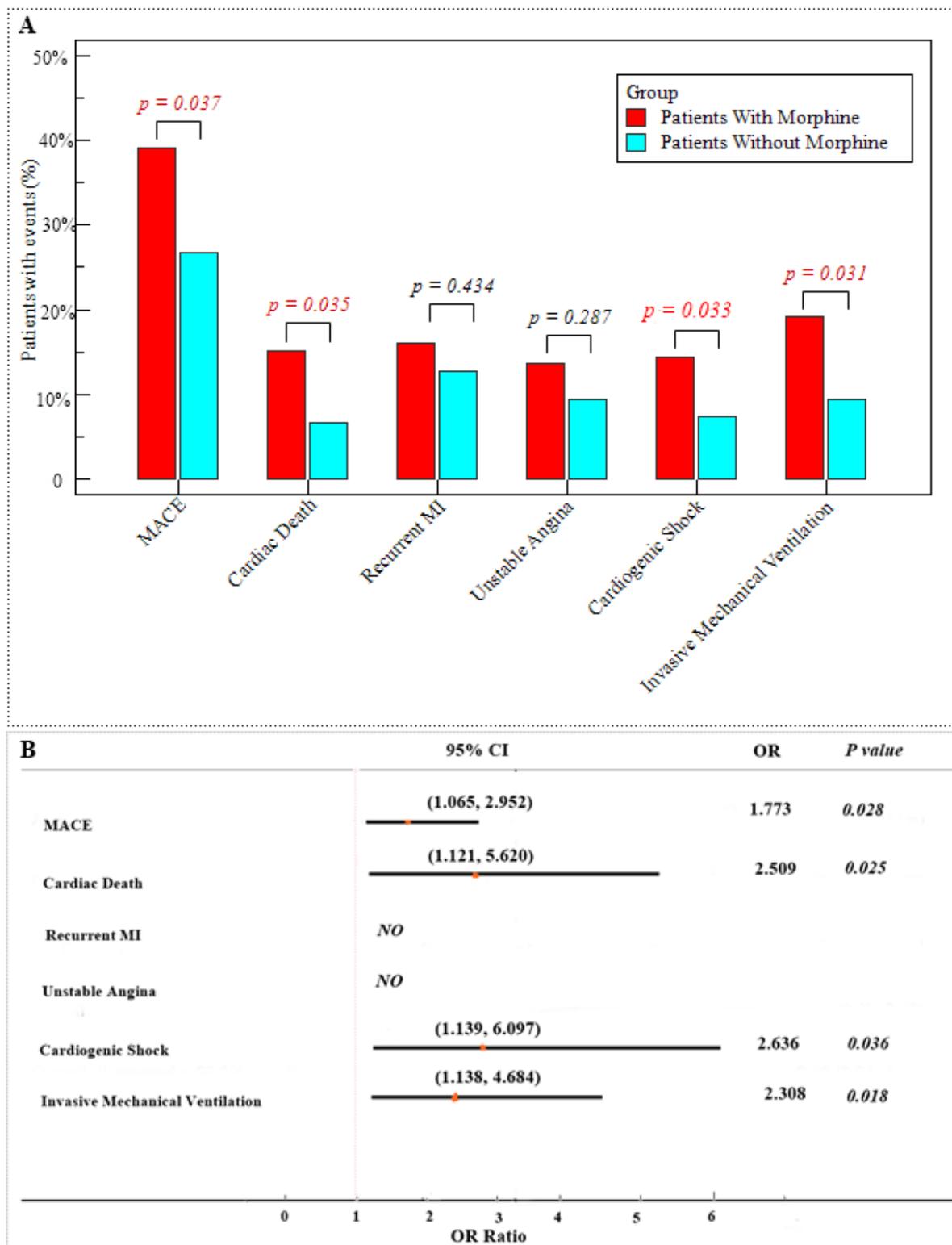


Figure 1

(A) Occurrence of major adverse cardiovascular events (MACEs) and individual events in-hospital. (B) Adjusted odds ratios (ORs) for the association of morphine use and outcomes by univariable analysis.

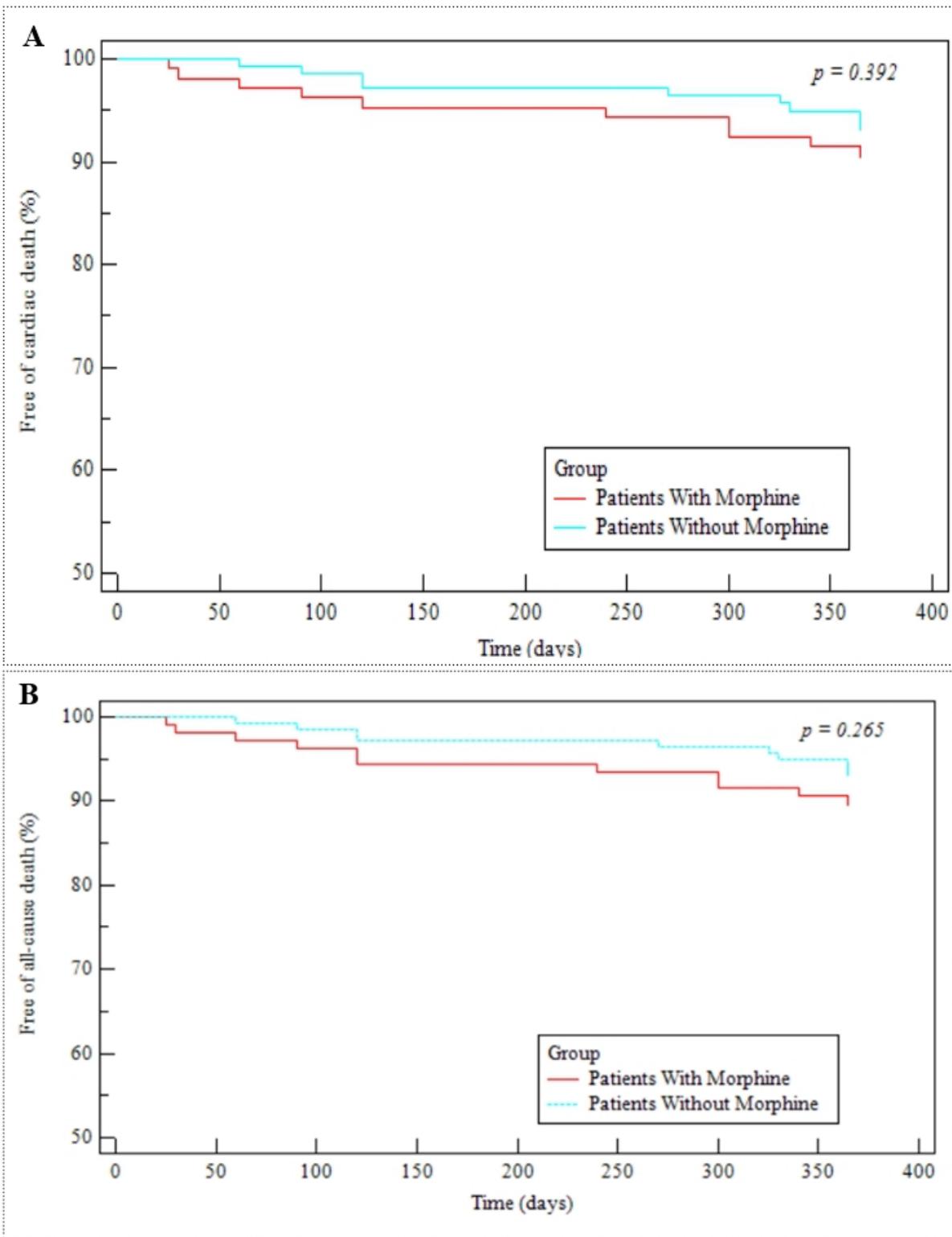


Figure 2

Kaplan–Meier curve analysis (log rank test) for survival free of cardiac death (A) and all-cause death (B) over 1 year of follow-up in the groups of STEMI and AHF patients treated with morphine and without morphine in-hospital.

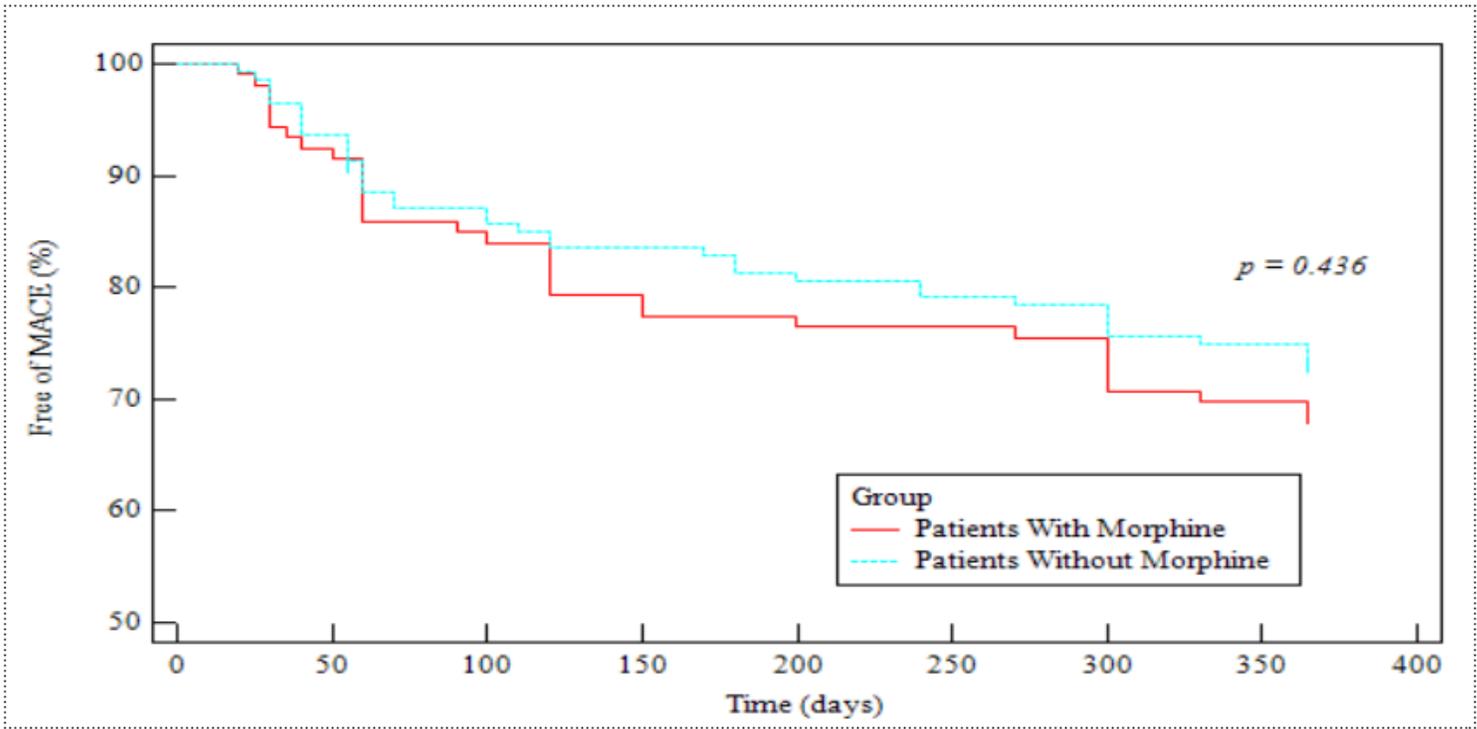


Figure 3

Kaplan–Meier curves for survival free of MACEs over 1 year of follow-up in the groups of STEMI and AHF patients treated with morphine and without morphine in-hospital.