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Morphine Use in the ED and Outcomes of Patients With Acute Heart Failure

A Propensity Score-Matching Analysis Based on the EAHFE Registry

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OBJECTIVE: The objective was to determine the relationship between short-term mortality and intravenous morphine use in ED patients who received a diagnosis of acute heart failure (AHF).

METHODS: Consecutive patients with AHF presenting to 34 Spanish EDs from 2011 to 2014 were eligible for inclusion. The subjects were divided into those with (M) or without IV morphine treatment (WOM) groups during ED stay. The primary outcome was 30-day all-cause mortality, and secondary outcomes were mortality at different intermediate time points, in-hospital mortality, and length of hospital stay. We generated a propensity score to match the M and WOM groups that were 1:1 according to 46 different epidemiological, baseline, clinical, and therapeutic factors. We investigated independent risk factors for 30-day mortality in patients receiving morphine.

RESULTS: We included 6,516 patients (mean age, 81 [SD, 10] years; 56% women): 416 (6.4%) in the M and 6,100 (93.6%) in the WOM group. Overall, 635 (9.7%; M, 26.7%; WOM, 8.6%) died by day 30. After propensity score matching, 275 paired patients constituted each group. Patients receiving morphine had a higher 30-day mortality (55 [20.0%] vs 35 [12.7%] deaths; hazard ratio, 1.66; 95% CI, 1.09-2.54; $P = .017$). In patients receiving morphine, death was directly related to glycemia ($P = .013$) and inversely related to the baseline Barthel index and systolic BP ($P = .021$) at ED arrival ($P = .021$). Mortality was increased at every intermediate time point, although the greatest risk was at the shortest time (at 3 days: 22 [8.0%] vs 7 [2.5%] deaths; OR, 3.33; 95% CI, 1.40-7.93; $P = .014$). In-hospital mortality did not increase (39 [14.2%] vs 26 [9.1%] deaths; OR, 1.65; 95% CI, 0.97-2.82; $P = .083$) and LOS did not differ between groups (median [interquartile range] in M, 8 [7]; WOM, 8 [6]; $P = .79$).

CONCLUSIONS: This propensity score-matched analysis suggests that the use of IV morphine in AHF could be associated with increased 30-day mortality. CHEST 2017; 152(4):821-832

KEY WORDS: acute heart failure; ED; morphine; opiates; outcome

ABBREVIATIONS: AHF = acute heart failure; HR = hazard ratio; IQR = interquartile range; LOS = length of stay; M = morphine; PS = propensity score; WOM = without morphine

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Morphine has largely been used to treat patients with acute heart failure (AHF) with the most severe forms of dyspnea, and especially in those presenting with acute pulmonary edema.[1,2] There are no large randomized controlled trials supporting the use of morphine in the treatment of patients with AHF. Physiological theory to support its use is made on the basis of favorable hemodynamic effects (reducing preload and, to a lesser extent, afterload) and beneficial CNS actions (relieving patient anxiety, breathlessness, restlessness, and chest pain).[3,4] However, these advantages may be overcome by negative hemodynamic effects, particularly in patients with previous volume depletion, as well as by deleterious CNS depression and a reduction in ventilatory drive, especially in patients with concurrent chronic respiratory disease.[3,4] In the scenario of AHF, therefore, the use of morphine remains largely controversial. The American Heart Association/American College of Cardiology only support the use of morphine for palliative care in end-stage heart failure.[5] The European Society of Cardiology does not recommend routine use of morphine, suggesting that it should only cautiously be used in patients with severe dyspnea, and predominately in those with pulmonary edema (recommendation class IIB; level of evidence B).[6] The main reason is the controversy regarding the potentially elevated risk of mortality in patients receiving morphine.[7-9] Considering the scarcity of data, we used propensity score (PS) techniques to evaluate a large registry of consecutive patients with AHF attended in the ED to ascertain whether morphine use is associated with short-term adverse outcomes.

Patients and Methods

Study Setting

The present study was carried out in patients included in the Epidemiology of Acute Heart Failure in Emergency Department (EAHFE) Registry. This is a multicenter, observational, multipurpose, cohort-designed database that includes consecutive patients who received a diagnosis of AHF in 34 Spanish EDs in both university and community hospitals from all areas of the country. The characteristics of the EAHFE Registry have been published elsewhere.[10-12] For the present study, we used patients included in the registry in 2011 (2 months of recruitment, 25 participating EDs, n = 3,414) and 2014 (2 months, 27 EDs, n = 3,233). The recruitment dynamics were the same in both periods. Briefly, patients were included by the attending emergency physicians, all of whom were given specific instructions about the study protocol during a meeting held the week before each recruitment period in every ED. All the cases identified were double-checked by the principal investigator of each center who was blinded to the treatment provided in the ED (including morphine) before inclusion into the database to ascertain whether patients fulfilled the clinical diagnostic criteria of AHF. In addition, when possible and available, the diagnosis was confirmed by natriuretic peptide determination or echocardiography following the European Society of Cardiology criteria during ED or hospitalization stay[6] (done in approximately 92% of cases). However, patients with clinical diagnostic criteria but without ECG or natriuretic peptide determinations were accepted to have a cohort as close as possible to what is observed in the routine emergency medicine practice. Final diagnostic adjudication was done by the principal investigator of the center. All principal investigators were provided with a dictionary of terms to ensure common definitions at all centers (e-Table 1). The only exclusion criterion in the EAHFE Registry was patients who received a primary diagnosis of ST elevation myocardial infarction who concurrently developed AHF (which occurred in approximately 3% of AHF cases).

Variables Analyzed

In every patient, we collected 46 variables potentially related to prognosis, including demographics, clinical history, presentation, and treatments on the basis of the authors' consensus after review of previous literature.[13-15] These variables were reported in specific case report forms during ED attendance (e-Table 1). Interventions, treatments, and patient allocation (hospital admission or discharge) were entirely on the basis of the decisions of the attending emergency physician. Subsequent follow-up by telephone contact and consultation of medical records was performed between days 31 and 90 after ED attendance to detect all-cause death.

The entire EAHFE Registry protocol was approved by a single central Ethical Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain; reference no. 49/2010). Because of the noninterventional design of the study, Spanish legislation allowed the remaining centers participating in a multicenter study to include patients with central Ethical Committee approval, after duly informing their local Ethical Committees about their participation. All patients gave informed consent to be contacted for follow-up. Around 2% of patients fulfilling the inclusion and exclusion criteria refused to participate and did not sign informed consent.

Statistical Analysis

The classificatory variable was the use of IV morphine during the first 3 hours after ED arrival; thus, patients were divided into two groups on

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the basis of whether they were treated with morphine (M) or without morphine (WOM). Thereafter, we investigated if there were any differences in the distribution of the 46 independent variables collected in the present study. With this proposal, we used χ^2 or the Student t tests (or Mann-Whitney U test when appropriate) depending on whether the variables were qualitative or quantitative, respectively.

After this first approach, we used PS matching analysis to analyze two comparable cohorts: with or without the use of morphine. A PS was estimated for each of the patients[16] using multivariate logistic regression. The PS determines the probability that participants would receive morphine on the basis of their individual characteristics (covariates). We constructed a multivariable model including the independent variables that significantly differed between groups (defined as a $P < .05$), as well as age and sex, which, a priori, the authors decided should be included irrespective of the P value. A PS was then obtained for every patient on the basis of discordant epidemiological, baseline, clinical, and therapeutic factors. This method provides accurate estimates of the effect of a drug in observational settings by minimizing confounding factors by indication[17] and has been proposed as a solution to overcome immortal time bias (from the patient's entrance into the cohort to the study drug intake) in pharmacologic and epidemiological studies.[18] Finally, patients were paired (1:1) on the basis of a maximum standardized difference of 1% in the PS.

The primary outcome of the present study was time to all-cause death within 30 days after admission in PS-matched patients. The primary end point was described using Kaplan-Meier survival curves, and we used a log-rank test to compare the two curves. Risk of all-cause death was calculated by estimation of hazard ratios (HRs) with 95% CI. Subgroup analyses of the primary outcome was planned a priori for sex, age, and use of vasoactive drugs (levosimendan, dopamine, dobutamine, or noradrenaline) or ventilatory support (noninvasive or invasive) in the ED; interaction was assessed by Cox models. As sensitivity analyses, we estimated the risk of all-cause mortality at 3, 7, and 14 days and in-hospital mortality (calculated by including both patients who died during hospitalization and while in the ED before hospitalization) by means of OR and their 95% CI. Additionally, differences in length of stay (LOS) were also calculated for hospitalized patients discharged alive. Finally, for patients included in the M group of the PS analysis, we investigated independent factors associated with the primary end point (30-day mortality) by including all variables with a statistically significant different distribution in the univariate analysis in a logistic regression model (enter mode). All statistical tests were performed with a two-sided type I error of 5%; we used statistical software (SPSS v 19.0) for all the calculations.

Results

Of the 6,647 patients initially included in the EAHFE Registry, 131 were excluded from analysis (49 without recorded morphine use and 82 lost to follow-up), leaving 6,516 for analysis in the present study. Overall, 416 patients (6%) were included in the M and 6,100 (94%) in the WOM groups (Fig 1). Comparisons between the two groups are presented in Table 1, with differences in 24 of the 46 baseline study variables. Patients in the M group had higher rates of ischemic heart disease, cerebrovascular disease, peripheral artery disease, and dementia, but were less likely to have chronic lung

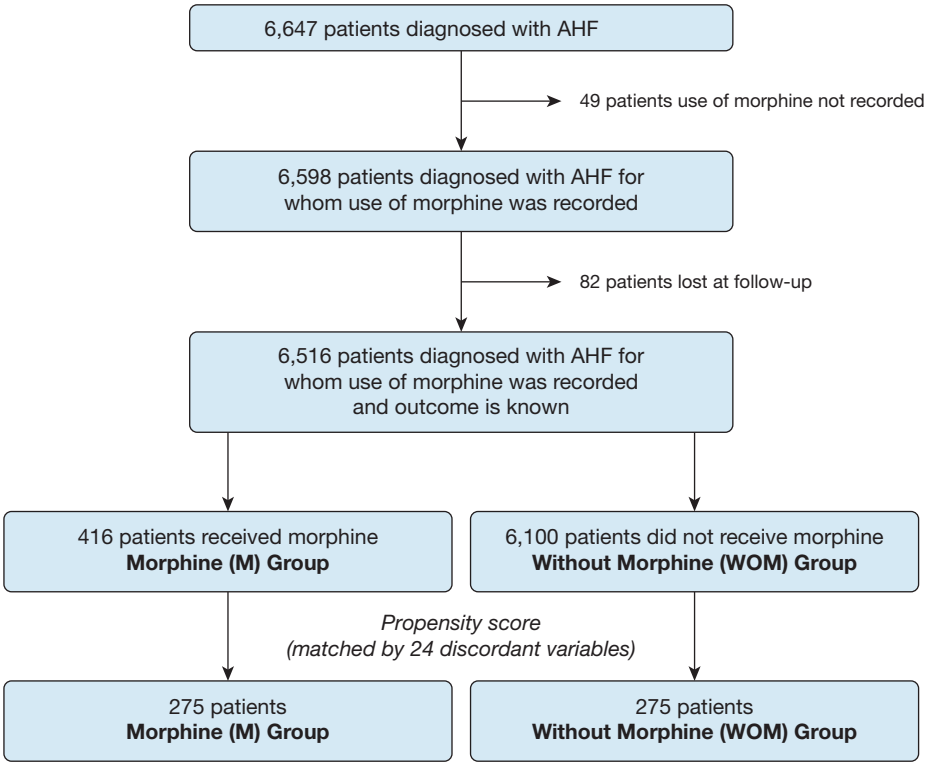


Figure 1 – *Flow chart of patient inclusion in the present study. AHF = acute heart failure.*

TABLE 1] Characteristics of the 6,516 Patients in the Raw Analysis of This Study and the 550 Patients Matched by a PS; Comparison Between Patients With M Who Died and Those Who Survived 30 d After the Index Event

		Raw Analysis			Propensity Analysis			Patients Treated With M		
	Total N = 6,516 No. (%)	M n = 416 No. (%)	WOM n = 6,100 No. (%)	*P* Value	M n = 275 No. (%)	WOM n = 275 No. (%)	*P* Value	Dead After 30 d n = 55 No. (%)	Alive After 30 d n = 220 No. (%)	*P* Value
Demographic data										
Age, mean (SD)	80.6 (9.8)	80.6 (10.2)	80.1 (9.9)	.33	80.7 (10.2)	81.1 (10.1)	.66	85 (9)	80 (10)	**.001**
Women	3,662 (56.4)	248 (59.9)	3,414 (56.1)	.15	118 (42.9)	117 (42.5)	1.00	32 (58.2)	125 (56.8)	.98
Comorbidities										
Arterial hypertension	5,513 (84.6)	347 (83.6)	5,166 (84.7)	.59	231 (84.0)	250 (90.9)	**.02**	47 (85.5)	184 (83.6)	.90
Diabetes mellitus	2,742 (42.1)	193 (46.5)	2,549 (41.8)	.07	126 (45.8)	140 (50.9)	.27	23 (41.8)	103 (46.8)	.61
Dyslipidemia	2,870 (44.1)	170 (41.0)	2,700 (44.3)	.20	108 (39.3)	129 (46.9)	.09	19 (34.5)	89 (40.5)	.52
Ischemic heart disease	1,948 (29.9)	153 (36.9)	1,795 (29.4)	**.002**	100 (36.4)	102 (37.1)	.93	18 (32.7)	82 (37.3)	.64
Chronic kidney failure	1,632 (25.1)	108 (26.1)	1,524 (25.0)	.66	72 (26.2)	71 (25.8)	1.00	17 (30.9)	55 (25.0)	.47
Cerebrovascular disease	871 (13.4)	80 (19.3)	791 (13.0)	**< .001**	50 (18.2)	48 (17.5)	.91	6 (10.9)	44 (20.0)	.17
Atrial fibrillation	3,166 (48.6)	158 (38.1)	3,008 (49.3)	**< .001**	123 (44.7)	108 (39.3)	.23	18 (32.7)	105 (47.7)	.06
Peripheral arterial disease	592 (9.1)	53 (12.8)	539 (8.8)	**.009**	42 (15.3)	32 (11.6)	.26	9 (16.4)	33 (15.0)	.97
Cardiac valve disease	1,840 (28.3)	116 (28.0)	1,724 (28.3)	.93	71 (25.8)	76 (27.6)	.70	13 (23.6)	58 (26.4)	.81
COPD	1,673 (25.7)	87 (21.0)	1,586 (26.0)	**.026**	60 (21.8)	58 (21.1)	.92	11 (20.0)	49 (22.3)	.85
Dementia	850 (13.1)	71 (17.1)	779 (12.8)	**.01**	41 (14.9)	44 (16.0)	.81	11 (20.0)	30 (13.6)	.33
Active cancer	859 (13.2)	63 (15.2)	796 (13.1)	.24	42 (15.3)	34 (12.4)	.39	9 (16.4)	33 (15.0)	.97
Prior episode of heart failure	3,764 (58.4)	241 (58.4)	3,523 (58.4)	1.00	162 (59.1)	167 (61.4)	.65	35 (63.6)	127 (58.0)	.54
Pacemaker or defibrillator	479 (7.7)	23 (6.4)	339 (7.8)	.36	17 (6.2)	21 (7.6)	.61	2 (3.6)	15 (6.8)	.57
Basal situation										
Barthel index points, mean (SD)	79 (24)	73 (28)	80 (24)	**< .001**	72 (29)	74 (26)	.30	54 (33)	77 (26)	**< .001**
Cardiorespiratory (NYHA III-IV)	1426 (23.8)	123 (31.7)	1,303 (23.3)	**< .001**	88 (32.1)	92 (33.5)	.81	25 (46.3)	62 (29.2)	**.03**
Chronic treatment at home										
Loop diuretics	4,276 (69.1)	210 (58.0)	4,066 (69.8)	**< .001**	168 (61.1)	171 (62.2)	.86	36 (65.5)	132 (60.0)	.56
Thiazide diuretics	792 (12.8)	49 (13.5)	743 (12.8)	.73	37 (13.5)	38 (13.8)	1.00	7 (12.7)	30 (13.6)	1.00
Aldosterone-receptor antagonists	1,123 (18.2)	52 (14.4)	1,071 (18.4)	.06	42 (15.3)	40 (14.5)	.90	6 (10.9)	36 (16.4)	.43
ACE inhibitor	2,007 (32.4)	113 (31.2)	1,894 (32.5)	.65	82 (29.8)	100 (36.4)	.12	13 (23.6)	69 (31.4)	.34

(Continued)

TABLE 1] *(Continued)*

	Total N = 6,516 No. (%)	Raw Analysis		*P* Value	Propensity Analysis		*P* Value	Patients Treated With M		*P* Value
		M n = 416 No. (%)	WOM n = 6,100 No. (%)		M n = 275 No. (%)	WOM n = 275 No. (%)		Dead After 30 d n = 55 No. (%)	Alive After 30 d n = 220 No. (%)	
Angiotensin-II receptor blocker	1,514 (24.5)	94 (26.0)	1,420 (24.4)	.54	76 (27.6)	70 (25.5)	.63	9 (16.4)	67 (30.5)	.06
Beta-blocker	2400 (38.8)	144 (39.8)	2,256 (38.7)	.74	106 (38.5)	104 (37.8)	.93	16 (29.1)	90 (40.9)	.14
Nitrates	1,144 (18.5)	91 (25.1)	1,053 (18.1)	**.001**	73 (26.5)	70 (25.5)	.85	16 (29.1)	57 (25.9)	.76
Digoxin	1,037 (16.8)	47 (13.0)	990 (17.0)	.05	42 (15.3)	40 (14.5)	.90	7 (12.7)	35 (15.9)	.71
Amiodarone	386 (6.2)	30 (8.3)	356 (6.1)	.12	23 (8.4)	12 (4.4)	.08	7 (12.7)	16 (7.3)	.30
Antiplatelets	2,339 (37.8)	158 (43.6)	2,181 (37.5)	**.02**	113 (41.1)	119 (43.3)	.65	23 (41.8)	90 (40.9)	1.00
Anticoagulants	1,446 (23.4)	63 (17.4)	1,363 (23.8)	**.006**	53 (19.3)	69 (25.1)	.12	15 (27.3)	38 (17.3)	.14
Vitals at ED arrival, mean (SD)										
Systolic BP (mm Hg)	142 (28)	152 (37)	141 (27)	**< .001**	153 (35)	154 (34)	.71	135 (36)	158 (33)	**< .001**
Heart rate (beats/min)	89 (25)	99 (27)	88 (24)	**< .001**	99 (28)	96 (25)	.20	89 (22)	101 (28)	**.004**
Basal oxygen saturation (%)	92 (7)	88 (24)	92 (6)	**< .001**	88 (9)	88 (11)	.82	85 (12)	89 (9)	**.001**
Temperature (°C)	36.2 (0.7)	36.2 (0.7)	36.2 (0.7)	.17	36.2 (0.6)	36.2 (0.6)	.44	36.3 (0.8)	36.2 (0.6)	.13
ECG										
Atrial fibrillation	3,047 (47.5)	158 (38.9)	2,889 (48.1)	**< .001**	120 (44.0)	114 (41.8)	.66	18 (32.1)	102 (46.8)	.08
Left ventricular hypertrophy	184 (2.9)	21 (5.2)	163 (2.7)	**.006**	14 (5.1)	6 (2.2)	.11	1 (1.8)	13 (6.0)	.36
Left or right bundle-branch block	579 (9.0)	66 (16.3)	513 (8.5)	**< .001**	49 (17.9)	31 (11.4)	.04	10 (18.2)	39 (17.9)	1.00
Laboratory results at ED, mean (SD)										
Glucose (mg/dL)	148 (68)	192 (87)	146 (67)	**< .001**	185 (81)	194 (101)	.27	206 (91)	180 (77)	**.03**
Creatinine clearance (mL/min/m^2)	59 (28)	54 (26)	60 (28)	< .001	56 (27)	58 (28)	.43	52 (23)	57 (28)	.29
Sodium (mmol/L)	138 (5)	138 (6)	138 (5)	.86	138 (6)	137 (5)	.17	137 (7)	138 (5)	.08
Potassium (mmol/L)	4.40 (0.67)	4.51 (0.80)	4.41 (0.68)	**.03**	4.48 (0.72)	4.47 (0.71)	.90	4.7 (0.9)	4.4 (0.7)	**.01**
Hemoglobin (g/L)	119 (20)	121 (21)	120 (21)	.26	122 (22)	119 (21)	.14	121 (21)	121 (21)	.84
Intensive treatment at ED										
IV nitrates	1,068 (16.4)	250 (60.1)	818 (13.4)	**< .001**	158 (57.5)	163 (59.3)	.73	19 (34.5)	139 (63.2)	**< .001**

(Continued)

TABLE 1] (Continued)

	Total N = 6,516 No. (%)	Raw Analysis			Propensity Analysis			Patients Treated With M		
		M n = 416 No. (%)	WOM n = 6,100 No. (%)	*P* Value	M n = 275 No. (%)	WOM n = 275 No. (%)	*P* Value	Dead After 30 d n = 55 No. (%)	Alive After 30 d n = 220 No. (%)	*P* Value
Need for inotropes/ vasopressors	137 (2.1)	29 (7.0)	97 (1.6)	**< .001**	18 (6.5)	8 (2.9)	.07	4 (7.3)	14 (6.4)	1.00
Noninvasive ventilation	442 (6.8)	164 (39.4)	278 (4.6)	**< .001**	90 (32.7)	80 (29.1)	.41	13 (23.6)	77 (35.0)	.15
Mechanical ventilation	269 (4.1)	12 (2.9)	257 (4.2)	.24	8 (2.9)	12 (4.4)	.50	2 (3.6)	6 (2.7)	1.00
Any kind of ventilatory support	692 (10.6)	170 (41.0)	522 (8.6)	**< .001**	93 (33.9)	90 (32.7)	.83	14 (25.5)	79 (36.1)	.18

Statistically significant *P* values are shown in bold. ACE = angiotensin-converting enzyme; M = morphine; NYHA = New York Heart Association; PS = propensity score; WOM = without morphine.

disease. They also showed a worse functional status, with a higher New York Heart Association class III-IV. In regard to outpatient treatment, patients in the M group less often received loop diuretics and anticoagulants, but more frequently received nitrates and antiplatelet agents. At ED arrival, systolic BP and heart rate were higher and room-air pulse oximetry lower in the M cohort. Patients in the M group more often had ECG findings of left ventricular hypertrophy and left or right bundle-branch block but less frequently had atrial fibrillation. Initial ED laboratory values of both glucose and potassium were higher, although creatinine values were lower in the M cohort. Finally, patients in the M group were more likely to receive IV nitrates, vasoactive drugs, noninvasive ventilation, and any kind of ventilatory support. In the entire cohort, 635 (9.7%) patients died within 30 days after ED attendance: 26.7% vs 8.6%, respectively, in the M and WOM groups ($P < .001$).

The PS was finally calculated using the 24 significant baseline variables; thus, the medians (interquartile range [IQR]) of the predicted probabilities of receiving morphine in patients in the M and WOM groups were 19.2% (39.9) and 2.1% (2.9), respectively ($P < .001$). On the basis of these predicted probabilities, PS matching provided 275 balanced paired cases. The only significant differences among these cases were the prevalence of arterial hypertension, which was more frequent in the WOM group, and right or left bundle-branch block, which was more frequent in the M group (Table 1). The medians of predicted probability of receiving morphine in the M and WOM PS-matched groups were 15.6% (IQR, 32.2) and 16.5% (IQR, 31.7), respectively ($P = .96$).

Overall, 90 patients (16.4%) died at 30 days in the PS-based analysis: 6 in the ED during the first 24 hours after ED arrival (five deaths from refractory heart failure and one from massive bleeding caused by overanticoagulation with acenocoumarol; these six patients had been previously ruled out for ICU admission because of comorbidity, severe baseline functional disabilities, and/or advanced age), two at home after direct discharge from the ED (one from refractory heart failure and one from hypovolemic shock); 56 died during hospital admission, and 26 died after hospital discharge. The six patients who died in the ED were in the M group ($P = .030$) (Table 2).

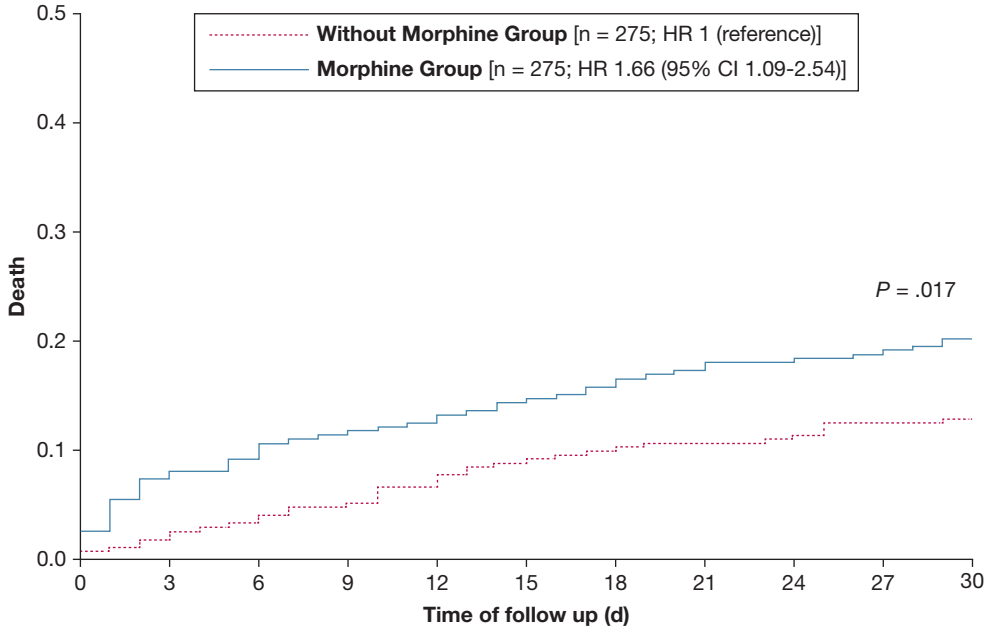
Among the 90 deaths, 55 were in the M group and 35 in the WOM group (20.0% vs 12.7%, respectively; $P = .028$). Survival analysis of the PS-matched patients showed a significant increase in 30-day mortality in the M group (HR, 1.66; 95% CI, 1.09-2.54; $P = .017$) (Fig 2),

TABLE 2] Description of Patients Who Died Included in the PS Analysis

	All Deaths (N = 90)	M Group (n = 55)	WOM Group (n = 35)
Specific conditions of M use			
M used during NIV (%)[a]	8 (9.4)	8 (16.0)	…
M used to treat ACS (%)[a]	6 (7.1)	6 (12.0)	…
Conceptual interval at which death occurred			
At ED (before hospitalization) (%)	6 (6.7)	6 (10.9)	0 (0)
After direct ED discharge (%)	2 (2.2)	2 (3.7)	0 (0)
During hospitalization (%)	56 (62.2)	32 (58.1)	24 (68.9)
After discharge from hospitalization (%)	26 (28.9)	15 (27.3)	11 (31.1)
Cause of death			
Refractory heart failure (%)	55 (61.1)	35 (63.6)	20 (57.1)
Other cardiovascular (%)	7 (7.7)	3 (5.5)	4 (11.4)
Noncardiovascular origin	15 (16.7)	6 (10.9)	9 (25.7)
Unknown (%)	13 (14.4)	11 (20.0)	2 (5.7)
Death at home (%)[b]	11 (12.4)	9 (16.4)	2 (5.9)

ACS = acute coronary syndrome; NIV = noninvasive ventilation. See Table 1 legend for expansion of other abbreviations.
[a]This information was not available in 5 patients.
[b]This information was not available in 1 patient.

and mortality was increased at 3, 7, and 14 days, with the greatest OR being found at the shortest post-ED time (8.0% vs 2.5%; OR, 3.33; 95% CI, 1.40-7.93; $P = .007$) of 3 days. In-hospital mortality in the M group was higher than in the WOM group, although without statistical significance (14.2% vs 9.1%; OR, 1.65; 95% CI, 0.97-2.82;



Without Morphine Group											
Events (death)	0	7	11	14	21	25	28	29	31	34	35
Remaining alive	275	268	264	261	254	250	247	246	244	240	239
Morphine Group											
Events (death)	0	22	29	32	36	40	45	49	50	52	55
Remaining alive	275	253	246	243	239	235	230	225	224	221	217

Figure 2 – *Analysis of primary outcome using survival curves for propensity score-matched patients treated with and without IV morphine in the ED. HR = hazard ratio.*

$P = .083$) (Fig 3). The median hospital LOS in the patients discharged alive did not differ between the M and WOM groups: 8 (IQR, 7) and 8 (IQR, 6) days ($P = .79$), respectively. Patients receiving morphine who died differed from those who survived in nine variables (Table 1). However, only 3 of these variables were independent predictors of 30-day mortality: glycemia ($P = .013$) had a direct relationship; the baseline Barthel index ($P = .021$) and systolic BP ($P = .021$) at ED arrival had an inverse relationship.

Preplanned subgroup analyses showed that the increased risk of short-term mortality only differed with respect to age, but not sex, and the use of vasoactive drugs or ventilatory support in the ED (Fig 4).

Discussion

On the basis of a PS-matched analysis, the most relevant finding of our study was that the use of IV morphine in patients with AHF in the ED is associated with a greater risk of 30-day mortality. We observed an increased risk of mortality at all the time points measured and found that the risk of death associated with morphine use was especially high at the shortest time points, as predicted by the pharmacokinetics of the drug. No relationship was found between morphine use in the ED and either in-hospital mortality or LOS in patients who survived hospital admission and were discharged.

Our results are in line with the latest recommendations of the American Heart Association/American College of Cardiology and European Society of Cardiology, which restrict the use of opiates in AHF.[5,6,19,20] In fact, during the past several years, international guidelines have moved from positions of opiate recommendation for well-defined clinical scenarios to this current position. The main reason for this shift in position is the lack of clinical trials investigating the effects of morphine use on patient outcomes.[21] together with studies that suggest an increased risk of mortality. Historically, data to support guideline recommendations were only obtained from small studies that were not adjusted for confounding factors, especially for the severity of AHF presentation. Because opiates were more frequently used in the setting of acute severe presentations, the increased mortality in this subgroup could not distinguish between an increased risk of death from severe disease or from treatment.[22-25] However, three larger studies have enlightened the current recommendations. In the largest study to date, Peacock et al[7] reported data from the Acute Decompensated Heart Failure Registry, including nearly 150,000 patients admitted to US acute care hospitals for AHF. Of these, 14% were treated with morphine at some point of time during hospitalization. Those treated with morphine showed a greater in-hospital mortality, even after risk adjustment and exclusion of ventilated patients (OR, 4.84; 95% CI, 4.52-5.18). Conversely, Gray et al[9] performed a secondary analysis of 1,052 patients included in the UK Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial carried out from 2003 to 2007. Although there was no correlation between the use of morphine and improvement in respiratory distress or patient-perceived breathlessness over the first hour, they failed to find any relationship between morphine and 7-day mortality.[9] Because the 3CPO study was undertaken in the emergency setting and included more severe forms of AHF, the conditions of morphine use might have differed from those of hospital admission, as suggested by the fact that 51% of the patients received morphine. Finally, in a retrospective analysis of 2,336 Israeli patients hospitalized in cardiology or internal medicine wards, 9% of whom received morphine, Iakobishvili et al[8] found an increased risk of in-hospital death (OR, 2.0; 95% CI, 1.1-3.5), which

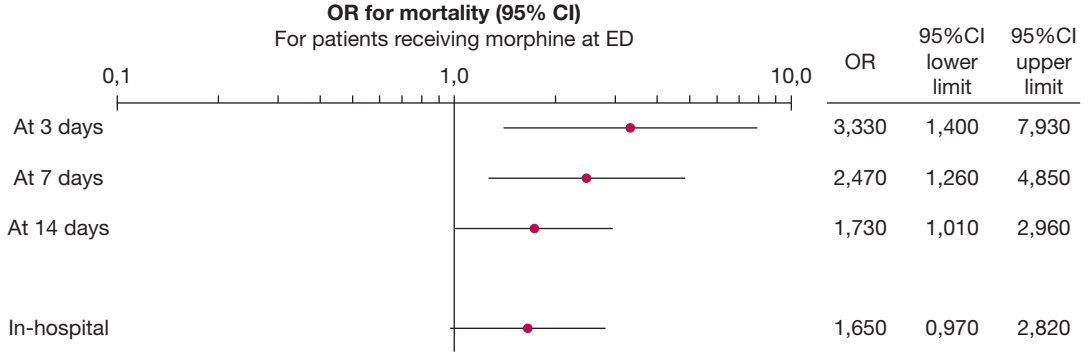


Figure 3 – *Analysis of secondary end points regarding intermediate mortality for propensity score-matched patients treated with and without IV morphine in the ED.*

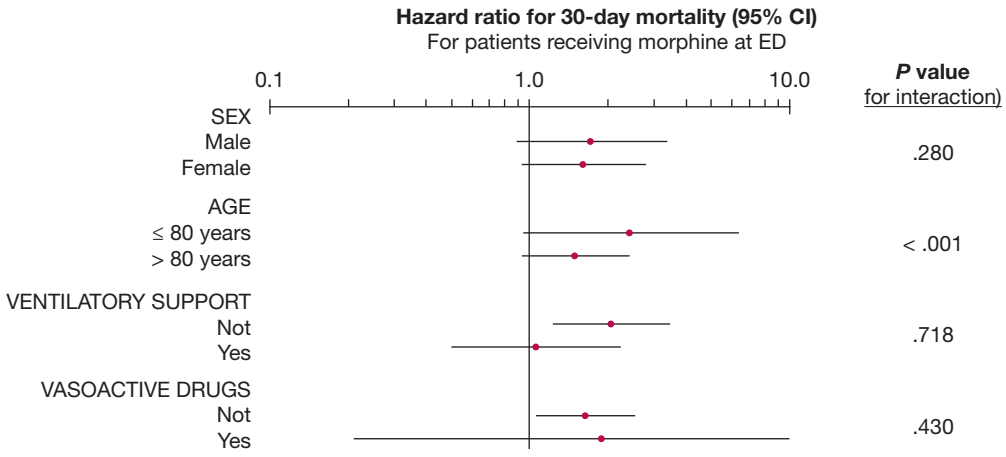


Figure 4 – *Sensitivity analysis stratifying 30-day mortality risk by sex, age, need for ventilatory support, and vasoactive drugs for propensity score-matched patients treated with and without IV morphine in the ED.*

did not remain significant after PS-matching of 218 paired patients (OR, 1.2; 95% CI, 0.6-2.4).

We believe that the current study adds some relevant insight to previous studies in the literature. First, it evaluates the effect of IV morphine in the emergency arena at very early stages of AHF treatment. This ED use of morphine may be markedly different than in admitted patients, in whom a fixed dose can be added. In the present study, we recorded the use of morphine in the ED during the first 3 hours of the initial patient treatment, at which time morphine is usually given in boluses as needed. Because the indication for morphine suggests that it is only administered to patients with the greatest disease severity, studies evaluating its usage are rarely approved, randomized, or placebo-controlled. This produces a scenario in which PS matching using retrospective data can provide insight and guidance to presentations for which there would be little evidence-based data. Second, we included all patients with AHF and not only those admitted to hospital. Because some patients can die early in the ED, before admission to hospital (as occurred in six of patients), analysis limited to admitted patients may incur some kind of bias. And third, because we included practically all types of patients who received a diagnosis of AHF (only those with ST elevation myocardial infarction were excluded in the present series) and not those specifically admitted to ICUs or cardiology wards (as occurs in other series), the patients analyzed in the present study corresponded to a population with substantial differences in the baseline characteristics and outcomes compared with those included in previous studies. Some authors have advocated this multidisciplinary approach, involving different specialties, because it would allow a wider spectrum of patients with heart failure to be covered.[26,27] It is well known that the aforementioned specialties admit younger patients, for whom there is usually no limitation in the therapeutic approaches implemented. Conversely, the universe of AHF (which is better represented in the ED, where practically all patients with a decompensation consult) includes patients with advanced forms of cardiomyopathy, severe functional impairment, and many comorbidities. Our sample is quite representative of this universe because the mean age of patients was 81 years, comorbidities were frequent, and up to 26% of patients had a Barthel index $<$ 60 (severe functional limitation), all being clearly higher than in the three previously mentioned studies in this same field.[7-9] In addition, most of the patients did not fulfill the criteria for ICU admission; this could explain why our mortality rates were higher than those described in previous studies.[7-9]

It is interesting to note that our results showed an increase in the overall short-term mortality but no changes in in-hospital mortality or hospital LOS. With respect to the first, there may have been a type II error, because PS matched only 275 pairs of patients, leaving quite a small sample size, and comparison of in-hospital mortality was close to demonstrating a significant increase, which would be in line with increased mortalities in short-term comparisons. With respect to hospital LOS, we believe that this could be partially influenced by the fact that, according to study definition, we included only patients admitted to hospital and discharged alive in the calculation of this secondary end point.

On the other hand, we found that some of the most severely ill patients died in the ED while awaiting a hospital bed, and none of these patients was considered a candidate for admission to an ICU. Although it was not recorded, compassionate morphine use may have been administered to some of these patients, which would explain the greater mortality observed in the early stage of AHF. Nonetheless, although the increase in the very short-term mortality (especially at 3 days) found in the present study could potentially be explained by physicians having given morphine to patients with greater baseline disease, PS matching should have identified a cohort with similar baseline risks. This suggests that morphine use may have some yet-to-be-identified mechanisms associated with short-term death. It remains unclear whether this is the result of a prolonged adverse cardiovascular effect, modulation of receptor sensitivity, respiratory drive inhibition, or chronic negative inotropic action. However, the net result is an association with short-term death (and especially with very short-term mortality at 3 days), which makes it difficult to support this therapy. It was also of note that we found an interaction with respect to age, and a higher mortality was associated with morphine use in patients with 80 years of age or younger. The possibility that the effects of morphine use are the most deleterious in patients most likely to survive (younger patients) is of great concern. On the other hand, once morphine is given, factors related to higher mortality were advanced age, limited baseline functional status (shown by the Barthel index), and decreased blood pressure at ED arrival, all of which are well-known general factors with an effect on the prognosis of patients with severe acute conditions.

Although this is one of the largest evaluations of the use of morphine in AHF to date, it has important limitations. First, as a retrospective uncontrolled evaluation, insight into our conclusion must be limited to the generation of hypotheses but, remarkably, our results are consistent with prior AHF analyses suggesting that, in the absence of a documented benefit, routine morphine use should be avoided. Second, in 8% of patients, a diagnosis of AHF was exclusively on the basis of clinical criteria, but this is a pragmatic approach that reproduces what is happening in many EDs worldwide. Third, the total dose of morphine administered to each patient was not quantified; thus, we could not determine whether the higher mortality rate was related to higher doses of morphine. Fourth, although we were able to identify the use of morphine in patients with chest pain or those undergoing noninvasive ventilation, we failed to identify whether morphine use was palliative in some cases. However, because we only recorded the use of morphine during the first 3 hours after patient arrival to the ED, palliative use was most likely low. Fifth, as in any study carried out in a single country, extrapolation of the results at an international level should be made with caution. Additionally, Spanish EDs participating in the EAHFE Registry were not randomly selected, but rather were members of the Acute Heart Failure Study Group of the Spanish Society of Emergency Medicine research network, with special interest in AHF; thus, the results could differ when applied to other EDs. Sixth, PSs are widely used to overcome the bias shown in observational studies when a specific treatment is analyzed because they match the population according to the main covariates. The PS is a validated method for the identification of trends, but strong conclusions cannot be made because hidden confounders in some covariates may not be included in the analysis; therefore, the results with this methodology should be taken with caution and considered, as in the present study, as the generation of a hypothesis that should be confirmed in clinical trials. Indeed, a current ongoing randomized clinical trial could eventually answer this question.[28]

In conclusion, our data suggest that the use of morphine in ED patients who have received a diagnosis of AHF is associated with an increased 30-day mortality, and that this increased risk is especially higher during the first 3 days. With few data to support the use of morphine in this cohort, we suggest that its use in AHF patients should be curtailed until further data demonstrating safety become available.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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