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Adverse dose-dependent effects of morphine therapy in acute heart failure

Oren Caspi, Robert Naami, Elya Halfin, Doron Aronson *

Department of Cardiology, Rambam Medical Center, B. Rappaport Faculty of Medicine, Technion Medical School, Haifa, Israel

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ABSTRACT

Background: Morphine has been a pivotal therapy in acute heart failure (AHF) for more than a century. The evidence for morphine therapy in AHF remains controversial. This study sought to assess the therapeutic effect of morphine on patients with AHF.
Methods: The study used a cohort of 13,788 patients admitted with a primary diagnosis of AHF. Propensity-score-matching was generated using 26 clinical variables. Primary endpoints included in-hospital mortality and invasive mechanical ventilation. Secondary endpoints included non-invasive ventilation, need for inotropes and acute kidney injury (AKI).
Results: 761 (5.5%) patients were treated with morphine in the first day following hospital admission. Propensity score matching yielded 672 patient pairs. The incidence of invasive ventilation was higher in the morphine-treated patients (7.4%) than in matched patients in the no-morphine cohort (3.6%), OR 2.13 (95% CI 1.32–3.57, $P = 0.007$). In-hospital mortality was also higher in the morphine group (17.4%) than in the matched no-morphine group (13.4%), OR 1.43 (95% CI 1.05 to 1.98, $P = 0.024$). For both the endpoint of invasive ventilation ($P_{\mathbf{trend}} = 0.005$) and mortality ($P_{\mathbf{trend}} = 0.004$), there was a significant linear dose-response relationship for the adverse effect of morphine. Morphine was associated with a significant increase in all secondary outcomes: Non-invasive ventilation (OR 2.78, 95% CI 1.95–3.96); Inotrope use (OR 3.50, 95% CI 2.10–5.82) and AKI (OR 1.81, 95% CI 1.39–2.36). A landmark analysis demonstrated no difference in post-discharge survival between cohorts.
Conclusions: Morphine administration is associated with significant dose-dependent risk for in-hospital mortality and need for mechanical ventilation.

1. Introduction

Morphine has been a pivotal therapy in acute heart failure (AHF) for many decades, especially for patients presenting with pulmonary edema [1]. This common practice was mainly supported by the perceived physiological benefits of morphine and did not rely on randomized clinical trials. The beneficial physiological effects ascribed to morphine include anxiolytic effect, amelioration of dyspnea, reduction of the activity of the sympathetic nervous and vasodilatory effect promoting primarily preload reduction [2,3]. However, morphine therapy in AHF has several potential hazardous effects including respiratory depression with hypoxia and CO_2 retention, hypotension, bradycardia as well as nausea and vomiting that may increase the risk for aspiration [4,5].

Retrospective studies from the last decade raised doubts regarding the efficacy and safety of morphine therapy in AHF. In a large retrospective study including patients from the ADHERE registry, morphine therapy was associated with a marked increase in hospital mortality (odds ratio 4.8), a higher rate of mechanical ventilation, intensive care admissions and longer duration of hospital stay [6].

A significant limitation of any nonrandomized analysis of the effect of morphine in AHF is that morphine-treated patients represent a cohort with more severe illness and would have been predicted to have a greater mortality. Studies using a smaller population of patients but applying propensity score matching (PSM) to partially address this problem, found contradicting results regarding morphine therapy and in-hospital outcomes [7,8].

Given that previous reports on the use of morphine in the setting of AHF resulted in conflicting conclusions [6–9], we aimed at evaluating the role of morphine in AHF by using a large propensity-matched cohort of AHF patients. We also sought to determine whether morphine dose affects clinical outcomes.

2. Methods

We used a database of all patients admitted to the Rambam Medical Center, Haifa, Israel with the primary diagnosis of AHF between January 2005 and Dec 2016. Eligible patients were those hospitalized with new-onset or worsening of preexisting heart failure as the primary cause of admission [10,11], using the European Society of Cardiology criteria

* Corresponding author at: Department of Cardiology, Rambam Medical Center, POB 9602, Haifa 31096, Israel.
E-mail address: daronson@technion.ac.il (D. Aronson).

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[12]. The study was performed in accordance with the Declaration of Helsinki and approved by the institutional review committee on human research.

Patients with morphine administration during the initial 24 h from hospital admission (entry to the emergency department) were included in the Morphine cohort. Patients treated by morphine after 24 h during the index hospitalization were excluded from the study. Missing data was not imputed. In addition, patients treated with morphine for palliative purposes were excluded.

2.1. Endpoints

The primary endpoints included invasive ventilation during the index hospitalization and in-hospital mortality. The secondary endpoints included non-invasive ventilation, need for inotrope or vasopressor therapy (dopamine, dobutamine, epinephrine, milrinone, norepinephrine, neosynephrin or vasopressin) and acute kidney injury (AKI). AKI was defined as an increase in serum creatinine concentration of ≥0.5 mg/dL compared with admission value. All endpoints were obtained by manually reviewing each patient's medical record.

2.2. Statistical analysis

Continuous variables are presented as mean ± SD or medians (with interquartile ranges), and categorical variables as numbers and percentages. Baseline characteristics of the unmatched groups were compared using unpaired *t*-test for continuous variables and by the χ^2 statistic for noncontinuous variables. After propensity-score matching, the baseline covariates were compared between the 2 groups with a paired *t*-test or Wilcoxon signed rank test for continuous variables and the McNemar test or marginal homogeneity test for categorical variables.

Because the clinical characteristics of patients treated with morphine differed markedly from those not treated with morphine, propensity score estimates representing the probability of a patient being treated with morphine were generated using a nonparsimonious multiple logistic regression model derived from clinical and laboratory parameters covariate available prior to the treatment assignment [13]. Following propensity score generation, patients were matched by using 1:1 nearest neighbor (Greedy-type) matching without replacement and a caliper width of a 0.2 standard deviation of the propensity score logit. Matching was performed without replacement, and nonmatched results were discarded.

We assessed the success of the matches by examining standardized differences (measured in percentage points) in the observed confounders between the matched morphine/no morphine groups. Small (<10%) standardized differences support the assumption of balance between groups based on observed confounders [14].

To estimate the treatment effects associated with morphine administration, we used methods that account for the matched nature of the sample. Accordingly, logistic generalized estimating equations (GEE) modeling were used to assess the effect of morphine exposure on the clinical outcomes in the propensity score–matched subpopulation [14,15]. Three prespecified subgroup analyses were performed by testing potential effect modification of mean arterial blood pressure, LVEF, and lactate levels with regard to the combined endpoint of invasive ventilation or in-hospital mortality.

To provide insight into differences in the potential early effects of morphine administration and the long-term prognostication associated with the group treated by morphine, we performed a landmark survival analysis [16] with a landmark set at hospital discharge. Patients whose survival is shorter than the Landmark point (in our case those who died at during hospitalization) are excluded from subsequent analysis. Surviving patients are then followed for 1 year to establish whether the prognostic factor (i.e., morphine use) had a significant effect on clinical outcome after hospital discharge. The rationale for selection of the hospital discharge cut-point for the landmark analyses was to separate early events that could be attributed to morphine use and post-discharge events unlikely to be a consequence of morphine use.

Cox proportional hazards model stratified by pair (to account for dependence among matched subjects) [14] was used to assess the risk of 1-year mortality after hospital discharge in patients with and without morphine treatment. Differences were considered statistically significant at the 2-sided $P < 0.05$ level. Statistical analyses were performed using STATA Version 15.1 (College Station, TX).

3. Results

A total of 13,788 patients were enrolled in the registry, and 761 of those (5.5%) were treated with morphine during the first 24 h of admission. The baseline clinical and characteristics of the study population prior to matching are shown in Table 1, Left panel. Some differences, such as older age and more comorbidities including hypertension, prior myocardial infarction and diabetes, and lower sodium levels suggested higher risk in the morphine group overall. In addition, morphine-treated patients presented with higher blood pressure and heart rate, higher white blood cell count and glucose levels, suggesting a greater degree of acute stress. Prior therapy with antiplatelet agents, ACE-inhibitors, and beta-blockers was more frequent in the morphine group.

Propensity-score matching of the overall cohort yielded a total of 672 patient pairs. After PSM, patients were well balanced with respect to the variables included in the propensity model, with absolute standard differences between <10% (Fig. 1). In the matched cohort, there were no significant differences between the groups (Table 1, Right panel).

Left ventricular ejection fraction (available in 938 patients of the matched cohort, 70%) was also similar between the groups (47% ± 18% vs. 46% ± 19%, $P = 0.34$). Baseline lactate levels (prior to morphine administration in the treated group) were available in 535 pairs and were similar between the groups (2.4 ± 1.6 mmol/L vs. 2.5 ± 1.7 mmol/L, $P = 0.37$). The oxygen saturation (measured with or without oxygen supplementation) was comparable in patients treated with morphine compared with patients who were not treated with morphine (92 ± 8% vs. 93 ± 7%, $P = 0.051$). Brain natriuretic peptide levels were available in 246 pairs (1140 ± 986 vs. 1159 ± 936 ng/ml with and without morphine, respectively, $P = 0.44$).

Other drugs administered concomitantly with morphine included intravenous furosemide (mean initial dose 57 ± 27 mg and 67 ± 31 mg in patients with and without morphine therapy, respectively ($P < 0.0001$)). IV Nitrates were administered in a minority of patients albeit more in the morphine group: 39 (5.8%) and 17 (2.5%) of patients with and without morphine therapy, respectively ($P = 0.003$).

3.1. Effect of morphine on the primary endpoints

Following PSM, the incidence of invasive ventilation was higher in the morphine-treated patients (50 events, 7.4%) than in matched patients who were not treated with morphine (24 events, 3.6%). Compared with the control group, the OR for the need for invasive ventilation was 2.13 in the morphine-treated patients (95% CI 1.30 to 3.50, $P = 0.003$). In-hospital mortality was also higher in the morphine group (OR 1.43, 95% CI 1.05–1.96, $P = 0.024$; Table 2).

The mean morphine dose in the treated group was 5 ± 4 mg. We tested a potential dose-dependent relationship between morphine dose and clinical outcomes by comparing patient receiving morphine dose of ≤5 mg (n = 427) and >5 mg (n = 245) to the control group. For both the endpoint of invasive ventilation ($P_{\mathbf{trend}} = 0.005$) and mortality ($P_{\mathbf{trend}} = 0.004$), there was a significant linear dose-dependency for the adverse effect of morphine (Fig. 2).

Because splitting the morphine group may reduce render the matching less robust, we also analyzed the dose-response relationship between morphine and clinical outcome using unconditional logistic regression, adjusting for all the variables in Table 1 [17]. Compared with the control group, the adjusted OR for invasive ventilation or mortality was 1.48 for patients receiving ≤5 mg of morphine [95% CI 1.05–2.09, $P = 0.03$] and 1.96 for patients receiving >5 mg of morphine [95% CI 1.32–2.90, $P = 0.001$] ($P_{\mathbf{trend}} = 0.008$).

3.2. Effect of morphine on secondary endpoints

More adverse outcomes occurred in the morphine cohort, including higher rates of non-invasive ventilation and a marked increase in the need for inotropic support (Table 2). In addition, AKI (defined as an increase in serum creatinine >0.5 mg/dL) occurred more frequently in the morphine-treated patients.

3.3. Subgroup analyses

We performed 3 prespecified subgroup analyses, testing potential effect modification of mean arterial blood pressure, LVEF, and lactate levels with regard to the combined endpoint of invasive ventilation or in-hospital mortality. The effect of morphine on the need for invasive ventilation or in hospital mortality was similar in patient with mean blood pressure below or above 100 mm Hg ($P_{\mathbf{interaction}} = 0.38$), in

Table 1
Baseline clinical characteristics in unmatched and propensity-matched patients.

Characteristics	Before propensity-matching			After propensity-matching		
	No morphine (n = 13,027)	Morphine (n = 761)	*P* value	No morphine (n = 672)	Morphine (n = 672)	*P* value
Age (years)	75 ± 12	78 ± 11	<0.0001	78 ± 11	78 ± 11	0.60
Male	6502 (50)	319 (42)	<0.0001	274 (41)	277 (41)	0.17
Hypertension	8340 (64)	568 (75)	<0.0001	505 (75)	508 (76)	0.85
Diabetes	6844 (53)	411 (54)	0.43	361 (54)	369 (55)	0.66
Prior myocardial infarction	2574 (20)	224 (29)	<0.0001	177 (26)	189 (28)	0.44
Chronic lung disease	1830 (11)	102 (13)	0.69	90 (13)	99 (13)	1.00
Atrial fibrillation	5520 (42)	312 (41)	0.46	281 (42)	276 (41)	0.78
Valvular heart disease	1727 (13)	74 (9)	0.005	74 (11)	67 (10)	0.53
Systolic blood pressure (mm Hg)	145 ± 33	154 ± 37	<0.0001	153 ± 32	154 ± 37	0.72
Heart rate (beats/min)	83 ± 20	91 ± 22	<0.0001	91 ± 22	91 ± 22	0.95
Serum creatinine (mg/dL)	1.7 ± 1.2	1.7 ± 1.2	0.63	1.8 ± 1.5	1.7 ± 1.2	0.33
Serum BUN (mg/dL)	35 ± 33	36 ± 21	0.64	37 ± 22	36 ± 21	0.34
eGFR ($ml \cdot min^{-1}/1.73\ m^{-2}$)	48 ± 26	46 ± 30	0.02	45 ± 23	46 ± 31	0.39
Glucose	172 ± 85	212 ± 101	<0.0001	203 ± 97	207 ± 99	0.43
Serum sodium	137 ± 5	136 ± 5	0.006	137 + 5	137 ± 5	0.48
Serum potassium	4.3 ± 0.7	4.4 ± 0.7	0.02	4.4 ± 0.6	4.4 ± 0.7	0.60
Baseline hemoglobin (g/dL)	11.5 ± 2.0	11.6 ± 2.0	0.91	11.5 ± 1.9	11.5 ± 2.0	0.57
White blood cell count	10.2 ± 7.4	12.9 ± 6.2	<0.0001	12.9 ± 10.2	12.4 ± 5.4	0.28
Temperature at admission (°C)	36.7 ± 0.5	36.7 ± 0.6	0.78	36.7 ± 0.6	36.7 ± 0.6	0.47
Background medical therapy						
Antiplatelet agents	4337 (33)	307 (40)	<0.0001	237 (41)	273 (41)	1.00
Beta blockers	8837 (68)	572 (75)	<0.0001	497 (74)	508 (76)	0.49
ACE inhibitors/A-II blockers	7887 (61)	499 (66)	0.006	427 (64)	437 (65)	0.56
Furosemide	8095 (62)	481 (63)	0.56	400 (60)	431 (64)	0.09
MRA	1533 (12)	69 (7)	0.02	51 (8)	64 (10)	0.20
Metolazone	226 (1.7)	11 (1)	0.55	8 (1)	9 (1)	0.81
Anticoagulants	3587 (28)	205 (27)	0.72	180 (27)	179 (27)	0.95

Data are number (%) or mean ± SD; For the matched group comparisons were done with paired *t*-tests or the McNemar's test.

patients with LVEF above or below 45% ($P_{\text{interaction}} = 0.52$), and in patients with lactate levels above or below 2 mmol/L ($P_{\text{interaction}} = 0.88$).

3.4. Morphine and post-discharge outcome

A landmark analysis of post-discharge mortality and readmission for heart failure was performed using the 1139 patients who survived the index hospitalization (584 and 555 patients with and without morphine therapy, respectively). The 1-year Kaplan-Meier estimates for the combined endpoint of HF readmission or death rates were 0.36 [95% CI 0.33–0.41] and 0.34 [95% CI 0.30–0.38] with and without morphine therapy (Supplementary Fig. 3), with a hazard ratio of 1.11 (95% CI 0.93–1.33, $P = 0.32$) in the morphine-treated patients compared with the control group.

4. Discussion

The present study is a contemporary retrospective analysis evaluating the outcome of morphine-treated patients in the setting of AHF. The study demonstrates that morphine administration early after admission is associated with increased risk for in-hospital mortality and need for mechanical ventilation. Furthermore, morphine therapy was associated with additional adverse outcome within the index hospitalization including a higher need for non-invasive ventilation, increased AKI rates, and increased use of inotropic support. The association between morphine therapy and adverse clinical outcomes was further strengthened by the demonstration of a dose-dependent relationship of morphine with each of the primary endpoints. Finally, a landmark analysis demonstrated that the risk associated with morphine therapy was confined to the index hospitalization.

The use of opiates in acute heart failure dates back to the 19th century [18]. The effects of morphine on anxiety and dyspnea relief are generally believed to be beneficial [19–21]. Additional hemodynamic benefits frequently cited include the reduction in of venous tone with pooling of blood in the systemic circulation, peripheral arteriolar dilatation and antisympathetic effects [19,22–24]. In particular, morphine-induced reduction in of venous tone is considered advantageous in the setting of pulmonary edema. This would lead to reduced venous return to the right heart and reduced right ventricular output, allowing the failing left ventricle to operate at a lower filling pressure, but may also lead to decreased cardiac output and hypotension, particularly with concomitant pulmonary hypertension.

However, there is little compelling evidence, that morphine causes either clinically significant venous pooling in the systemic circulation [25,26] or a meaningful reduction of left or right ventricular filling pressures [3,27,28]. By contrast, the results of the present study demonstrate the potential adverse hemodynamic effects of morphine. We observed a marked increase in the use of inotropic support after morphine administration, as well as increased AKI rates, likely due to a hemodynamic compromise.

Whereas the hemodynamic benefits of morphine remain questionable, [3,27,28] opioids are known to decrease both hypoxic and hypercapnic respiratory drive and induction of sedation and respiratory depression are among the most serious complications. Opioids are second in the classes of medications contributing to adverse-event reporting for hospitalized patients, with sedation and respiratory depression being among the most commonly reported adverse effects [29]. Our study is in-line with previous reports finding an association between morphine administration and increased use of invasive ventilation and mortality [6,30]. Importantly, the current study demonstrates a dose-dependent increase in the occurrence of these adverse outcomes. The presence of a dose-dependent effect further strengthens the association between morphine administration and the evaluated adverse outcomes. Remarkably, the use of morphine was associated with increased risk for invasive ventilation even in low doses (≤5 mg).

The results of previous retrospective studies evaluating the effects of morphine in AHF remain controversial. A study based on the ADHERE registry demonstrated a strong association between morphine therapy and mortality, strong even after risk adjustments and exclusion of ventilated patients (OR of 4.84 for mortality) [6]. The study was limited by the fact that morphine dosage and timing of administration were not available. In contrast, a study based on an Israeli registry of AHF (with

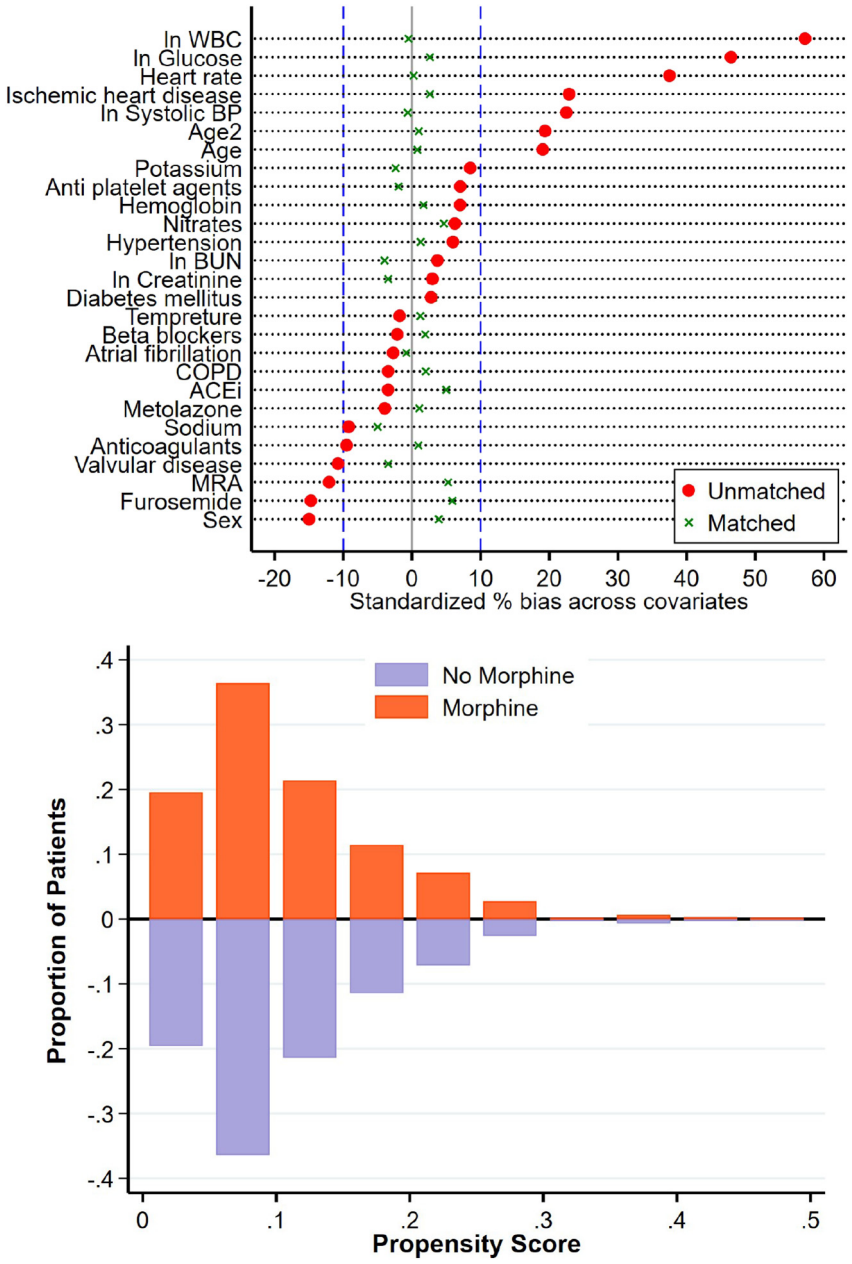

Fig. 1. A. Covariable balance before (red circles) and after (green exes) matching. The standardized difference after propensity matching (blue lines) are all well within 10%. B. Mirrored histogram of distribution of propensity scores for morphine-treated patients (Morphine; bars above the zero line) vs no-morphine (bars below the zero line).

two thirds of morphine-treated patients having an acute coronary syndrome) showed that in a multivariate analysis morphine was associated with increased in-hospital mortality, but after conducting PSM, this effect was rendered insignificant [7]. In addition, an analysis from the 3CPO trial did not identify a relationship between opiate administration and mortality. However, opiate administration was independently associated with less improvement in arterial pH and did not improve breathlessness [9]. Recently, a study based on the Spanish EAHFE

Table 2
In-hospital events.

Event	No Mo n (%)	Mo n (%)	Odds ratio (95% CI) Morphine use compared with its non-use	*P* value
Primary endpoints				
Invasive ventilation	24 (3.6)	50 (7.4)	2.13 (1.30–3.50)	0.003
In-hospital mortality	88 (13.4)	117 (17.4)	1.43 (1.05–1.96)	0.024
Secondary endpoints				
Non-invasive ventilation	55 (8.2)	129 (19.3)	2.78 (1.95–3.96)	<0.0001
Inotropes use	23 (3.4)	70 (10.5)	3.50 (2.10–5.82)	<0.0001
Acute kidney injury	120 (17.9)	188 (28.0)	1.81 (1.39–2.36)	<0.0001

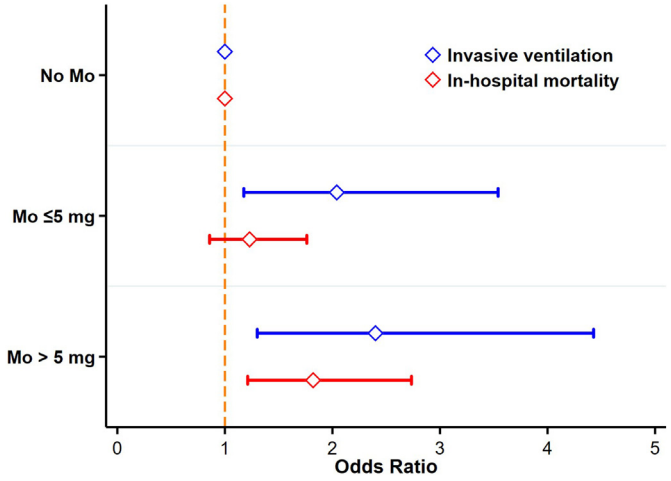

Fig. 2. Odds ratios (and 95% confidence intervals) for invasive ventilation (blue) and in-hospital mortality (red) according to morphine dose. The reference group includes patients who did not receive morphine.

registry which included 275 propensity score matched patients, reported that morphine therapy during emergency department stay was associated with increased 30-day mortality, with a hazard ratio of 1.66 [8]. In the present study, we observed that in-hospital mortality increased in a dose-dependent manner with morphine therapy. Of note, the magnitude of the mortality increase associated with morphine was much smaller than reported by Peacock et al. [6] and approximated the report of Miró et al. [8]

One critique raised over previous studies [31] is that the adverse outcome associated with morphine in AHF may have been related to the use of morphine as a palliative treatment for terminal patients the AHF hospitalization. In order to avoid this potential bias, the current study excludes patients with alternative indications for morphine administration. In addition, our cohort did not include patients with a primary diagnosis of myocardial infarction, therefore, allowing us to assess the consequences of morphine therapy on patients presenting with AHF.

Although morphine therapy is not currently encouraged by the European guidelines [12] it is still frequently used [32]. The continued use of morphine may be attributed to the rapid initial anxiolytic effects, which may also be perceived as symptomatic relief. Some physicians believe that morphine associated harmful effects may be restricted only to specific high-risk groups such as those with hypoperfusion, low LVEF, or CO_2 retention. Therefore, major contemporary literature advises a cautious use of morphine for these specific groups [20,33]. Our study demonstrates the lack of effect modification even for patients with high MAP (MAP>100 mmHg), LVEF>45% and those with normal lactate levels (<2 mmol/L), suggesting similar hazard of morphine therapy in these subgroups. Importantly, the rationale to identify subgroups that might be benefited from morphine therapy when the overall results show harm is not plausible [34]. Therefore, morphine can be viewed as potentially hazardous to all AHF patients.

4.1. Study limitations

The study herein is a retrospective study, and as such is subject to several limitations. Morphine administration prior to the arrival at the emergency department may have not been consistently reported. However, expected bias associated with such treatment misclassification would lead, in anything, to the reduction of the relative hazard associated with morphine use.

A certain degree of residual imbalance between treated and untreated subjects in the matched samples is a potential concern. If such an imbalance existed, with the morphine-treated patient being at higher risk than matched controls, we should expect an increased rate of heart failure readmissions and mortality in the morphine-treated group that persists after hospital discharge. The results of the landmark analysis provide further reassurance that the matched group were indeed balanced with regard to prognostically important covariates. However, PSM cannot substitute a prospective randomized controlled trial. The ongoing MIMO trial will evaluate if midazolam is a better anxiolytic than morphine for AHF [35].

4.2. Conclusions

Based on an analysis of a large single-center cohort of AHF patients, morphine administration is associated with significant dose-dependent risk for in-hospital mortality and need for mechanical ventilation, as well as with hemodynamic deterioration. The current study results are consistent with recent clinical guidelines raising concerns with regard to morphine administration in AHF. The initial immediate anxiolytic effects must be balanced against the risk of respiratory deterioration and increased mortality.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.015.

Declaration of Competing Interest

None.

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