

Milrinone is associated with lower in hospital mortality in patients with cardiogenic shock: a retrospective analysis of the MIMIC-III database

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Research

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Abstract

Background

Although milrinone has been widely used in daily clinical practice, its effect on survival in patients with cardiogenic shock (CS) is not known. The primary purpose of this study was to evaluate the effectiveness of milrinone on in-hospital mortality in a large critical care cohort of patients with CS of various etiological causes.

Methods

Patients with CS were identified from the Medical Information Mart for Intensive Care III (MIMIC-III) database. Propensity score matching (PSM) was used to account for the baseline differences in the probability to receive milrinone or not. Multivariate Cox regression model was employed to adjust for imbalance by including parameters and potential confounders.

Results

A total of 1068 critically ill patients with CS were enrolled for this analysis, including 161 in the milrinone group and 907 in the non-milrinone group. Multivariate Cox regression model results found milrinone was associated with a significantly decreased in-hospital mortality in critically ill patients with CS (HR 0.61, 95% CI 0.45-0.83; $P=0.001$). The impact of milrinone on survival benefit in CS was remaining in patients with non-ACS, while it was not statistically significant in subgroup with ACS (HR 0.66, 95% CI 0.40-1.07; $P=0.093$). Similar results were replicated after PSM.

Conclusions

Our study observed that milrinone was related with improved survival in patients with CS, but it was not associated with improved outcome in patients complicated with ACS. The results need to be verified in randomized controlled trials.

Introduction

The prognosis of cardiogenic shock (CS) remains poor, despite advances in pharmacological and mechanical circulatory support[1-7]. Inotropes are often initiated immediately for hemodynamic support in CS, usually coadministration with a vasoconstrictor, to increase cardiac output, and restore perfusion[8-10]. At present, the use of inotropic agents in patients with CS is given class IIb recommendation in current guidelines[11,12], primarily based on low quality of evidence and high risk of bias data.

Milrinone, a phosphodiesterase 3 (PDE3) inhibitor with inotropic and vasodilating actions, is of interest in CS for its improvement of cardiac output without increasing oxygen requirements[13]. Even the administration of milrinone for patients with CS is common in daily practice, the investigation with clarified clinical outcome is still lacking. In one recent Cochrane systematic review assessing inotropic

agents on CS, the included studies were of no milrinone treatment group[14]. Data from a large pooled retrospective analysis supported that the addition of an inodilator to vasopressors was associated with lower mortality, however, only 1% patients treated with PDE3 inhibitors[15]. Furthermore, co-interventions with other vasoactive medications, and mechanical circulatory support (MCS) might also have obscured the effects of milrinone.

Thus, we analyzed the real-world use of milrinone in a large critical care cohort of patients with CS of various etiological causes. The effect of milrinone on in hospital mortality in critically ill patients with CS was assessed.

Methods

Setting

Data were obtained from the Medical Information Mart for Intensive Care III version 1.4 (MIMIC-III, Version 1.4), which is a public and freely-available intensive care unit (ICU) database[16]. Briefly, the MIMIC-III database contains comprehensive, time-stamped information for more than 60,000 ICU patients (medical, surgical, coronary care and neonatal) admitted to Beth Israel Deaconess Medical Center (Boston, MA, USA) from June 1st 2001 to October 31st 2012 (single center), representing more than 46000 patients. Since the database was approved by the Institutional Review Boards (IRB) of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA), IRB approval from our institution was exempted. The study was reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement[17].

Study subjects

Patients for this study were selected from all persons in MIMIC-III aged ≥ 18 years at ICU admission with cardiogenic shock (ICD-9-CM diagnosis codes 785.51 or 998.01), plus any of the following criteria: minimum systolic blood pressure (SBP) < 90 mmHg, or need of vasopressors therapy (any of dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin), or signs of hypoperfusion (first 24 hours of urine output < 400 ml or maximum blood lactate > 2 mmol/L). Of these patients, we excluded patients with ≤ 0 days or ≥ 100 days between ICU admission and discharge, defined as the earliest of recorded ICU discharge, hospital discharge or time of death. Patients initiated milrinone therapy after 48 hours of ICU entry were also excluded. If patients who had multiple admissions to ICU, only the first ICU admission was included for analysis.

Demographical and laboratory variables

The following variables were extracted from the MIMIC-III database for the first day of ICU admission: age at the time of hospital admission, gender, acute coronary syndrome (ACS), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPSII), maximum creatinine, maximum bilirubin, maximum INR (international normalized ratio), mean heart rate, mean of mean BP (blood pressure),

minimum SBP, urine output first day after ICU entry, use of mechanical circulatory support (MCS), dobutamine, vasopressors, mechanical ventilation, and renal replacement therapy (RRT). If a variable was measured more than once in the first 24 hours, the maximum value was used. Patients with age ≥ 300 years was corrected as a median age of 91.4 years.

The primary endpoint was the hospital mortality, which was defined as the status of patient survival at the time of hospital discharge.

Statistical analysis

The study population was categorized into the milrinone (intervention) and non-milrinone (control) groups according to milrinone treating status after ICU entry. Categorical variables were expressed as the number of percentage. They were compared between milrinone and non-milrinone groups with Chi-square or Fisher's exact test as appropriate. Continuous variables were expressed as mean (standard deviation) or median [interquartile range (IQR)] as appropriate.

We selected these potential confounders on the basis of their associations with the outcomes of interest or a change in effect estimate of $>10\%$ or P-values <0.1 in univariable analyses. Cox regression model was used to adjust for imbalance by including parameters and potential confounders judged by clinical expertise.

Propensity score matching (PSM) was estimated with the use of a nonparsimonious multivariable cox-regression model[18], with CS with the use of milrinone as the dependent variable and select the baseline characteristics that was included in the multivariable cox regression model (including age, gender, APsIII, SAPsII, ACS, maximum creatinine, using MCS, mechanical ventilation, RRT, dobutamine, and vasopressors) as covariates. Matching was performed with the use of a 1:2 matching protocol with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.

A two tailed P value <0.05 was considered to be statistically significant. EmpowerStats version 2.17.8 (<http://www.empowerstats.com/cn/>) and R software version 3.42 were used for all statistical analysis.

Results

Subject characteristics

The initial search identified 61051 ICU admissions from the MIMIC-III database. A total of 1068 critically ill patients with CS were eligible for this analysis. Of the study cohort, 161 patients were exposed to intravenous milrinone treatment (milrinone group), and the remaining 907 did not receive milrinone (non-milrinone group) (Figure 1).

Table 1 shows the baseline characteristics for milrinone and non-milrinone groups. There were balanced baseline measures between the two treatment groups, including the severity of illness scores (APsIII and SAPsII), gender, mean of mean BP, urine output first day, maximum creatinine, maximum bilirubin,

maximum INR, and using RRT. More patients receiving milrinone were complicated with ACS, while had higher level of maximum lactate and mean heart rate. In the milrinone group, patients were older, and more likely using MCS, mechanical ventilation, and vasopressors, than in the non-milrinone group. Dobutamine was less used in milrinone group than in non-milrinone group.

Effect of milrinone on in hospital mortality in CS

Kaplan-Meier survival estimate was shown in Figure 2. During a mean length of hospital stay with 11.91 ± 11.26 days, patients in CS treated with milrinone were associated with improved survival ($P < 0.001$).

Multivariate Cox regression model results showed milrinone was associated with a significantly decreased in hospital mortality in critically ill patients with CS (HR 0.61, 95% CI 0.45-0.83; $P=0.001$), after adjusted for age, gender, AP3, SAPSII, ACS, maximum creatinine, using MCS, mechanical ventilation, RRT, dobutamine, and vasopressors.

Propensity score analysis

The 147 patients who received milrinone were matched to 294 patients who did not received milrinone by PSM. There were statistically significant imbalances of age, and mean heart rate between milrinone and non-milrinone groups. Since there were still residual imbalances, Cox proportional hazard model was used. The results showed that milrinone was still independently associated with improved survival in patients in CS (HR 0.55, 95% CI 0.39-0.78; $P<0.001$), adjusting for age, mean heart rate.

Subgroup analysis for milrinone on in hospital mortality in CS

There were 51.97% patients in CS complicated with ACS. Subgroup analyses were conducted among patients with ACS and non-ACS, as shown in Figure 3.

The impact of milrinone on lowering hospital mortality in CS was remaining in patients with non-ACS (HR 0.56, 95% CI 0.38-0.84; $P=0.004$), while was not statistically significant in subgroup with ACS (HR 0.66, 95% CI 0.40-1.07; $P=0.093$). After PSM, the survival benefit was consistently not significant in patients with ACS (HR 0.73, 95% CI 0.42-1.27; $P=0.272$).

Discussion

In the present retrospective study, data on the endpoint of in hospital mortality showing that milrinone has clear benefit on CS, with consistent result before and after PSM. Using of milrinone for CS conferred significant lower risk of in hospital mortality with HR of 0.61 before matching and HR of 0.55 after matching. However, the survival benefit of milrinone on CS was not statistically significant in patients with ACS.

Using milrinone in acute heart failure (AHF) patients without evidence of decreased organ perfusion is not appropriate, with previous clinical trials[19-22] have failed to show any benefit from this agent. In patients

with CS, the role of milrinone on mortality was not evaluated in randomized controlled trial, as shown in a recent updated Cochrane review[14]. Prospective observational multinational CardShock study[23] has specially assessed the efficacy of vasoactive medications on 90-day mortality in CS, subgroup analysis demonstrating that patients receiving PDE3 inhibitors (milrinone or enoximone) was neutrally associated with mortality. One small retrospective observational study[24] has compared the effectiveness of milrinone to dobutamine in CS, and found similar in hospital mortality between the two groups. In a large propensity-score analysis of three pooled observational datasets, Pirracchio et al[15] has provided evidence of survival benefit of inodilators in CS, however, only 1% patients treated with PDE 3 inhibitors. In the present study, we extracted data from the MIMIC-III critical care database and a total of 1068 patients with cardiogenic shock were included for comprehensive analysis. After multivariate Cox regression analysis, we found that giving milrinone was independently associated with lower risk of in hospital mortality for patients with CS, both before and after PSM.

Compared to previous studies on AHF, the severest manifestation of AHF populations in our study might be the primary reason for explanation of the survival benefit of milrinone. In the ADHERE (Acute Decompensated HEart Failure National Registry) registry[20], less than 3% had low systolic blood pressure. In OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure)[21], patients in CS were excluded. Moreover, the mean severity of illness scores were high in our study, with APsIII of 58.33 ± 23.26 and SAPSII 47.84 ± 15.47 , respectively. This severity was also reflected by poor survival rate, with in hospital mortality rate of 40.64% in our cohort while it was around 10% in both ADHERE and OPTIME-CHF.

In our study, subgroup analysis showed that the survival benefit of milrinone on CS was not seen in patients with ACS. Meanwhile, in a post hoc subgroup analysis[19], in which patients with an ischemic etiology of HF who received milrinone were related with increased mortality. By contrast, in a large retrospective study with few patients receiving PDE3 inhibitors, the positive survival outcome of inodilator (45% dobutamine, 10% levosimendan) remained unaltered in the subgroups of patients with or without an ACS. These results together highlight the caution is needed when milrinone is prescribed for patients with ischemic etiology in CS.

Several limitations were worthy of mention. Above all, the lack of randomization and used data from a single center in the USA, which may lead to selection bias. However, the included patients were of robust balanced baseline characteristics and multivariable Cox regression results were consistent before and after PSM. Second, adverse effects of milrinone were not evaluated in the present study. Although it is difficult to extract information on adverse events by using MIMIC-III database, this can be assessed in prospective randomized trials. Finally, only in hospital mortality was used, and this may affect the assessment of long-term prognosis.

Conclusions

In conclusion, in this large cohort of patients with CS, treated with milrinone, as compared with non-milrinone, was associated with lower in hospital mortality. However, this survival benefit was not seen in patients complicated with ACS. These findings should be prospective evaluation by randomized controlled trial.

List Of Abbreviations

CS: cardiogenic shock

PDE3: phosphodiesterase 3

MCS: mechanical circulatory support

MIMIC-III: Medical Information Mart for Intensive Care III

ICU: intensive care unit

IRB: Institutional Review Boards

RECORD: REporting of studies Conducted using Observational Routinely collected health Data

ACS: acute coronary syndrome

APS III: Acute Physiology Score III

SAPSII: Simplified Acute Physiology Score II

INR: international normalized ratio

BP: blood pressure

RRT: renal replacement therapy

IQR: interquartile range

PSM: Propensity score matching

AHF: acute heart failure

ADHERE: Acute Decompensated HEart Failure National Registry

OPTIME-CHF: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure

Declarations

Ethics approval and consent to participate

Since the MIMIC-III database was approved by the Institutional Review Boards (IRB) of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA), IRB approval from our institution was exempted.

Consent for publication

Not Applicable.

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Authors' contributions

KTJ and MPC both take responsibility for (and is the guarantor of) the content of the manuscript, including the data and analysis. YJX and JSW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Baseline Characteristics before and after Propensity Score Matching*.

Characteristic	Total	Before Matching			After Matching		
		Non-MILRINONE (907)	MILRINONE (161)	P-value	Non-MILRINONE (294)	MILRINONE (147)	P-value
AGE, median (IQR), years	73.37 (62.30-81.48)	73.55 (62.72-82.35)	71.75 (61.03-79.70)	0.030	74.01 (65.58-82.27)	71.52 (61.23-79.84)	0.004
GENDER, Male (%)	622 (58.24%)	531 (58.54%)	91 (56.52%)	0.631	173 (58.84%)	82 (55.78%)	0.539
ACS, n (%)	555 (51.97%)	486 (53.58%)	69 (42.86%)	0.012	150 (51.02%)	69 (46.94%)	0.419
APSIII	58.33 ± 23.26	58.28 ± 23.34	58.57 ± 22.82	0.885	61.09 ± 22.80	58.17 ± 22.96	0.207
SAPSI	47.84 ± 15.47	47.65 ± 15.53	48.91 ± 15.15	0.343	50.33 ± 14.86	48.79 ± 15.24	0.310
MCS, n (%)	373 (34.93%)	293 (32.30%)	80 (49.69%)	<0.001	140 (47.62%)	66 (44.90%)	0.589
ECMO, n (%)	16 (1.50%)	11 (1.21%)	5 (3.11%)	0.079	4 (1.36%)	3 (2.04%)	0.691
IABP, n (%)	366 (34.27%)	287 (31.64%)	79 (49.07%)	<0.001	139 (47.28%)	66 (44.90%)	0.637
Dobutamine, n (%)	238 (22.28%)	218 (24.04%)	20 (12.42%)	0.001	42 (14.29%)	20 (13.61%)	0.846
Vasopressors, n (%)	858 (80.34%)	712 (78.50%)	146 (90.68%)	<0.001	260 (88.44%)	132 (89.80%)	0.668
Dopamine, n (%)	483 (45.22%)	433 (47.74%)	50 (31.06%)	<0.001	158 (53.74%)	45 (30.61%)	<0.001
Epinephrine, n (%)	171 (16.01%)	89 (9.81%)	82 (50.93%)	<0.001	34 (11.56%)	72 (48.98%)	<0.001
Norepinephrine, n (%)	614 (57.49%)	495 (54.58%)	119 (73.91%)	<0.001	180 (61.22%)	105 (71.43%)	0.035
Phenylephrine, n (%)	378 (35.39%)	289 (31.86%)	89 (55.28%)	<0.001	105 (35.71%)	81 (55.10%)	<0.001
Vasopressin, n (%)	263 (24.63%)	182 (20.07%)	81 (50.31%)	<0.001	67 (22.79%)	69 (46.94%)	<0.001
Maximum Lactate, mmol/L	5.16 ± 4.25	5.01 ± 4.20	5.92 ± 4.44	0.021	5.20 ± 4.31	5.77 ± 4.56	0.239
Maximum Creatinine, mg/dL	2.13 ± 1.80	2.17 ± 1.86	1.90 ± 1.37	0.085	2.06 ± 1.36	1.93 ± 1.41	0.345
Maximum Bilirubin, mg/dL	1.38 ± 2.53	1.35 ± 2.68	1.55 ± 1.34	0.437	1.16 ± 2.09	1.43 ± 1.28	0.246
Maximum INR	2.26 ± 2.63	2.22 ± 2.57	2.47 ± 2.90	0.279	2.15 ± 1.84	2.48 ± 3.01	0.161
Mean Heart Rate, beats/minute	89.27 ± 17.25	88.37 ± 17.14	94.21 ± 17.11	<0.001	86.08 ± 16.75	94.14 ± 17.44	<0.001
Mean of Mean BP, mmHg	73.00 ± 10.13	73.22 ± 10.42	71.74 ± 8.26	0.087	72.35 ± 9.80	71.43 ± 8.33	0.334
Urine output first day, mL	1726.19 ± 1402.62	1721.72 ± 1395.14	1750.13 ± 1446.35	0.816	1716.44 ± 1384.70	1759.60 ± 1439.49	0.764
Mechanical Ventilation, n (%)	681 (63.76%)	559 (61.63%)	122 (75.78%)	<0.001	209 (71.09%)	108 (73.47%)	0.600
RRT, n (%)	81 (7.58%)	67 (7.39%)	14 (8.70%)	0.563	25 (8.50%)	11 (7.48%)	0.712

*Plus-minus values are means ±SD. IQR interquartile range, APSIII Acute Physiology Score III, SAPSI Simplified Acute Physiology Score II, MCS mechanical circulatory support, ECMO Extracorporeal membrane oxygenation, IABP intra-aortic balloon pump, INR international normalized ratio, BP blood pressure, RRT renal replacement therapy.

Table 2. Association of milrinone use and in hospital mortality by Cox regression before and after Propensity Score Matching

	Death, n(%)	HR (95% CI)	P value
Before Matching			
Univariable model			
non-milrinone	382 (42.12%)	1	
milrinone	52 (32.30%)	0.56 (0.42, 0.75)	<0.001
Multivariable model			
non-milrinone	382 (42.12%)	1	
milrinone	52 (32.30%)	0.61 (0.45, 0.83)	0.001
After Matching			
Multivariable model			
non-milrinone	123 (41.84%)	1	
milrinone	46 (31.29%)	0.58 (0.41, 0.83)	0.002

HR Hazard Ratio, CI confidence interval. Before matching, adjusted for age, gender, APACHE II, SAPS II, ACS, maximum creatinine, using MCS, mechanical ventilation, RRT, dobutamine, and vasopressors. After matching, adjusted for age, mean heart rate.

Figures

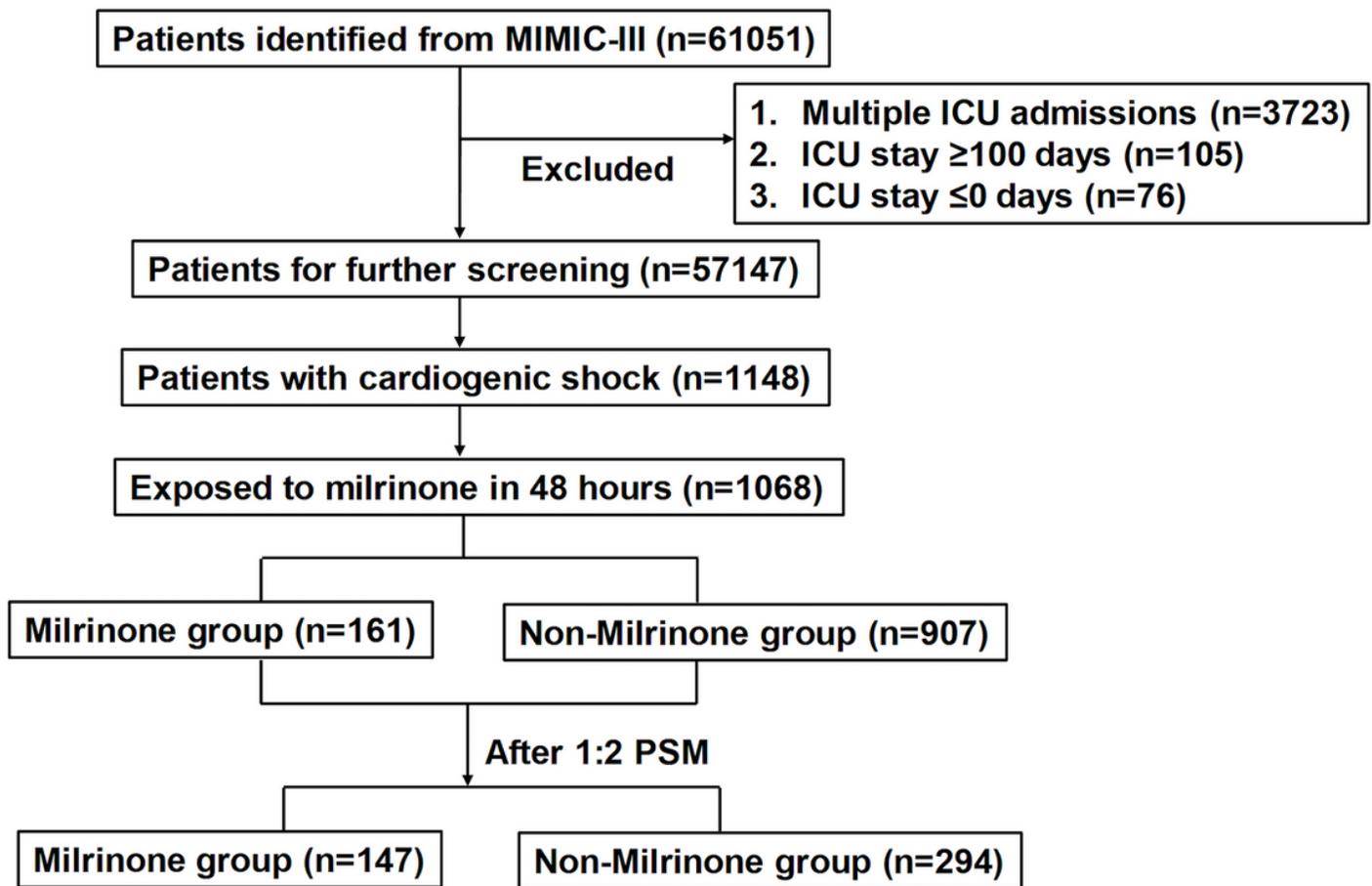


Figure 1

Flowchart of Patient Selection.

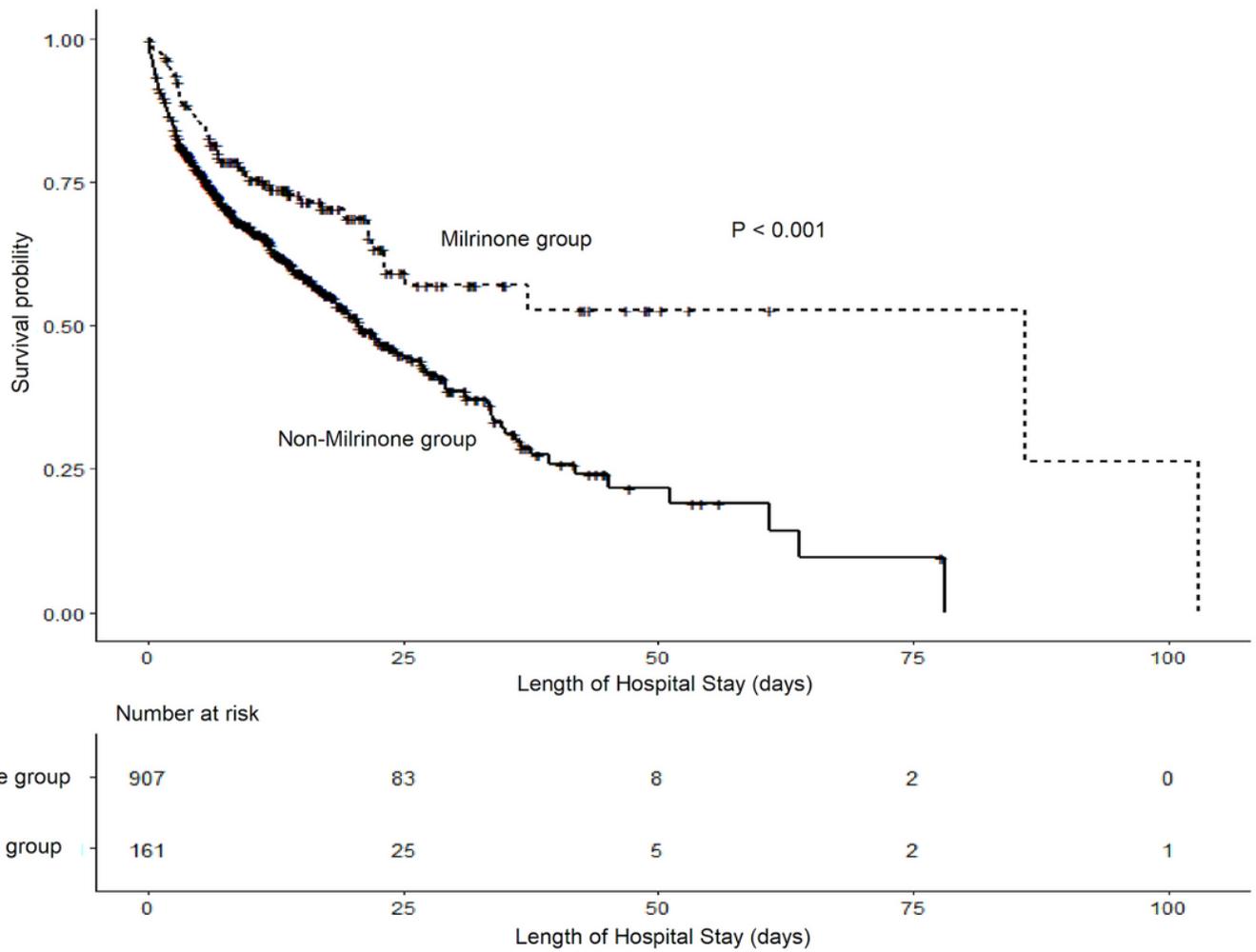


Figure 2

Kaplan-Meier Survival from in hospital mortality for patients in milrinone group and non-milrinone group.

Subgroups

Before Matching

HR (95% CI)

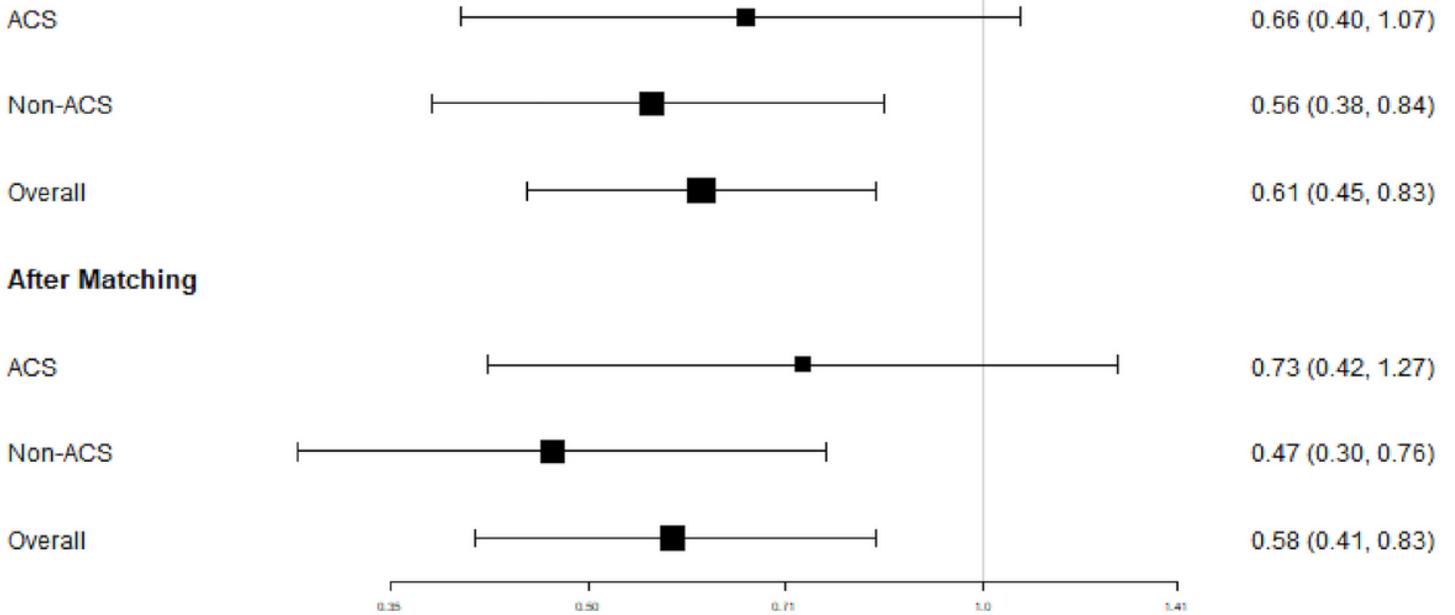


Figure 3

Subgroup analyses among patients with ACS and non-ACS before and after Propensity Score Matching (PSM).