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Effect of Dihydropyridine Calcium Channel Blocker on Mortality of Hypertension Patients With Moderate-Severe Pulmonary Acute Respiratory Distress Syndrome: A Multicenter Retrospective Observational Cohort Study

OBJECTIVES: The aim was to evaluate the effect of dihydropyridine calcium channel blocker on the prognosis for moderate-severe pulmonary acute respiratory distress syndrome in hypertension patients.

DESIGN: A retrospective, observational, multicenter cohort study.

SETTING: A total of 307 patients without propensity score matching and 186 adult inpatients with propensity score matching diagnosed with hypertension and moderate-severe pulmonary acute respiratory distress syndrome in five teaching hospitals in Jiangsu province, China, from December 2015 to December 2020 were enrolled.

PATIENTS: A total of 307 patients without propensity score matching and 186 patients with propensity score matching diagnosed with hypertension and moderate-severe pulmonary acute respiratory distress syndrome were included in the final analysis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Demographic characteristics and clinical characteristics were recorded. The propensity score matching method was used to eliminate the difference between group with dihydropyridine calcium channel blocker and group without dihydropyridine calcium channel blocker. The primary outcome was in-hospital mortality. We used univariate and multivariate regression analyses for both patients with or without propensity score matching to assess the effect of these variables on mortality. In the subset of 186 patients with propensity score matching, in-hospital mortality was 53.2%. Inpatient mortality was significantly higher in patients treated with dihydropyridine calcium channel blocker than in those not treated with dihydropyridine calcium channel blocker of patients without propensity score matching (65.4% vs 40.4%; $p < 0.01$). Multivariate analysis for patients without propensity score matching showed that dihydropyridine calcium channel blocker (hazard ratio, 1.954; 95% CI, 1.415–2.699), lactate dehydrogenase greater than or equal to 600 U/L (hazard ratio, 3.809; 95% CI, 2.106–4.531), and lactate greater than or equal to 2 mmol/L (hazard ratio, 1.454; 95% CI, 1.041–2.029) were independently associated with in-hospital mortality. Based on univariate analysis for patients with propensity score matching, dihydropyridine calcium channel blocker (hazard ratio, 2.021; 95% CI, 1.333–3.064), lactate dehydrogenase greater than or equal to 600 U/L (hazard ratio, 4.379; 95% CI, 2.642–7.257), and lactate greater than or equal to 2 mmol/L (hazard ratio, 2.461; 95% CI, 1.534–3.951) were independently associated with in-hospital mortality. In contrast, patients not treated with dihydropyridine calcium channel blocker had a significant survival advantage over those treated with dihydropyridine calcium channel blocker in both patients without or

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DOI: 10.1097/CCE.000000000000506

with propensity score matching ($p < 0.001$; $p = 0.001$ by Kaplan-Meier analysis).

CONCLUSIONS: Dihydropyridine calcium channel blocker, lactate dehydrogenase greater than or equal to 600 U/L, and lactate greater than or equal to 2 mmol/L at admission were independent risk factors for patients with hypertension and moderate-severe pulmonary acute respiratory distress syndrome.

KEY WORDS: acute respiratory distress syndrome; dihydropyridine calcium channel blocker; hypertension; mortality

Despite decades of increased attention to acute respiratory distress syndrome (ARDS), the morbidity and mortality of ARDS remain alarmingly high (1–3). With the aging of the population, the number of hypertensive patients with ARDS is increasing year by year. Patients with pulmonary hypertension who progress to ARDS have a higher mortality (4, 5).

A study from our group revealed that dihydropyridine calcium channel blocker (DCCB) aggravated acute hypoxia-induced pulmonary hypertension via activation of Ca^{2+} -sensing receptor (CaSR) in pulmonary artery smooth muscle cells (PASMCs) (6, 7). Increased intracellular Ca^{2+} fluxes during the activation of CaSR also played an important role in the contract of PASMC. Activation of CaSR is also related to a variety of functional outputs including cell proliferation, differentiation, and inflammation (8). Pulmonary hypertension is a common complication of ARDS (4). Severe ARDS will progress to pulmonary hypertension which plays a major role in the physiopathology of ARDS and is associated with an increased risk of mortality (9).

DCCB is commonly used as antihypertension medicine in China. However, no more than 5% of patients with pulmonary artery hypertension benefit from calcium channel blocker (CCB) in a long-term treatment (10). Evidence showed that DCCB further exacerbated pulmonary hypertension and increased right ventricular systolic blood pressure, leading to right ventricular hypertrophy (11, 12). CCB-induced neurohormonal sympathetic activation and sustained CCB-generated nitric oxide production could cause inflammation and tissue destruction (13). Patients with pulmonary hypertension treated with CCB for an extended period were prone to develop CCB-related peripheral edema,

which could reduce the patient compliance (14). CCBs have also been reported to suppress the functions of T cells and macrophages (15).

Therefore, it is necessary to detect whether DCCB could affect the prognosis of patients with hypertension combined with ARDS. Here, we conducted a retrospective cohort analysis of the multicenter to demonstrate the effect of DCCB on mortality of hypertensive patients with ARDS.

MATERIALS AND METHODS

Design, Setting, and Study Population

This retrospective study included all 376 adult inpatients (≥ 18 yr old) with a diagnosis of moderate-severe pulmonary ARDS and hypertension admitted to five teaching hospitals (The First Affiliated Hospital of Soochow University, Changshu No. 2 People's Hospital, Lianyungang Municipal Oriental Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, and The First People's Hospital of Kunshan) from December 2015 to December 2020 (16, 17). Both physician and investigators reviewed chest radiographs in agreement for the diagnosis of ARDS. We excluded the patients 1) who were immunosuppressed or had cancer, 2) who had hypertensive heart disease or (congestive) heart failure at admission, 3) who died or were discharged within 24 hours of receiving a diagnosis of ARDS, and 4) who lack data. Data of 307 patients were collected. A 1:1 propensity score matching (PSM) was used to match measured baseline characteristics of populations with DCCB treatment to comparator populations. Eventually, 186 patients were included in this study (**Fig. S1**, <http://links.lww.com/CCX/A748>). Based on the degree of hypoxemia, three mutually exclusive categories of ARDS were identified according to the Berlin definition: mild ($200 \text{ mm Hg} < \text{Pao}_2/\text{Fio}_2 \leq 300 \text{ mm Hg}$), moderate ($100 \text{ mm Hg} < \text{Pao}_2/\text{Fio}_2 \leq 200 \text{ mm Hg}$), and severe ($\text{Pao}_2/\text{Fio}_2 \leq 100 \text{ mm Hg}$) (16). Patients with risk factors of pneumonia or aspiration of gastric contents were categorized as pulmonary ARDS. Patients were categorized as hypertension grade I (140–159/90–99 mm Hg) and hypertension grade II ($\geq 160/\geq 100$ mm Hg) based on their highest mean blood pressure in a 4-week period (18, 19). DCCB therapy was defined as at least one kind of DCCB medication for more than 3 months. The regular dose of DCCB included in our study is felodipine

2.5 or 5 or 10 mg, amlodipine 5 or 10 mg, or nifedipine 30 or 60 mg. Mechanical ventilation strategies for patients were low-protective ventilation as supported by the ARDS Network trial (20). Spontaneous breathing trials and daily sedation interruptions were tried to eventually achieve unassisted breathing (21). This study was approved by the Committee for the Ethical Review of Research at The First Affiliated Hospital of Soochow University (IRB-2019050) and was conducted in accordance with institutional guidelines and the Declaration of Helsinki.

Data Collection

Demographic characteristics (age and gender) and clinical characteristics (comorbidities, laboratory findings, disease severity scores, treatment, complications, and outcomes) were recorded. Clinical data and chest radiographs are independently reviewed by two physicians to determine diagnostic accuracy. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated based on component variables during the first 24 hours after admission (22, 23).

Patients were followed up until discharge from hospital or death, whichever came first. The primary outcome of our study was defined as in-hospital mortality.

Statistical Analysis

Continuous data with a normal distribution are presented as mean \pm SD. If the continuous data are skewed, they are presented as median (interquartile range [IQR]). Frequency data are presented as proportions. According to the history of antihypertensive treatment, the patients were divided into with DCCB and without DCCB groups. A 1:1 PSM was used to reduce the selection bias of the two groups of baseline characteristics of populations with DCCB treatment to comparator populations. Propensity scores were calculated using Cox regression with the DCCB treatment cohort as the dependent variable and the following confounders initiation as independent variables: age, gender, smoke, alcohol, coronary artery disease, diabetes mellitus, $\text{PaO}_2/\text{FIO}_2$ ratio, albumin, lactate dehydrogenase (LDH), SOFA score, hemoglobin, and mechanical ventilation. C-statistics was used to evaluate the validity of PSM matching. For group without PSM, comparisons of continuous variables were made using Wilcoxon

rank-sum and chi-square by cohort, whereas in the matched data, Wilcoxon signed-rank and McNemar or Stuart-Maxwell tests for marginal homogeneity were used to compare baseline characteristics for continuous variables and proportions, respectively (**Table 1**).

Univariate Cox regression models were used to identify independent risk factors for in-hospital observed mortality. Variables with p value of less than 0.2 (**Table 2**) in the univariate analysis were included in the multivariate model (**Table 3**). Multivariate regression model was performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) to analyze the independent prognostic factors associated with mortality in hospitalized patients with hypertension and ARDS. Survival curves were plotted using the Kaplan-Meier method using the log-rank test and comparing both patients with and without DCCB treatment before and after PSM (**Fig. 1**). Data were analyzed using SPSS 25.0 (IBM, Chicago, IL). Excel 2016 (Microsoft) was used to prestatistical plot charts. A two-tailed p value of less than 0.05 was considered statistically significant.

RESULTS

Patients

Overall registry patient numbers and flow are shown in Figure S1 (<http://links.lww.com/CCX/A748>). Of the 376 patients diagnosed with hypertension and moderate-severe pulmonary ARDS, 12 patients were immunosuppressed or had cancer, 12 patients died within 24 hours of receiving the diagnosis of ARDS or had incomplete data, and 45 patients had hypertensive heart disease without (congestive) heart failure at admission were excluded. After matched by 1:1 PSM score, the final study included a total of 186 patients. As shown in Table 1, baseline characteristics of populations with PSM showed no evidence of a difference as confirmed by small standardized differences across DCCB treatment comparisons. Further, C-statistics was 0.74 for PSM.

In the univariate Cox regression model of group without PSM, gender, alcohol intake, with DCCB, LDH greater than or equal to 600 U/L, and lactate greater than or equal to 2 mmol/L were significantly associated with mortality (Table 3): with DCCB (HR, 1.954; 95% CI, 1.415–2.699; $p < 0.001$), LDH greater than or equal to 600 U/L (HR, 3.089; 95% CI, 2.106–4.531; $p < 0.001$), and lactate greater than or equal to 2

TABLE 1.**Comparison of Demographics and Clinicopathologic Characteristics of Unmatched and Matched Hospitalized Moderate-Severe Direct Acute Respiratory Distress Syndrome Patients With Hypertension With or Without the Dihydropyridine Calcium Channel Blocker Therapy**

Factors	Pre Matched			Post Matched		
	Without DCCB (N = 151)	With DCCB (N = 156)	p	Without DCCB (N = 93)	With DCCB (N = 93)	p
Male, %, n (%)	109 (72.2)	127 (81.4)	0.06	73 (78)	75 (81)	0.03
Age, median (interquartile ranges)	74.0 (65.0–82.0)	74.5 (67.0–79.0)	0.63	74.0 (66.0–78.0)	75.0 (67.0–81.0)	0.18
Smoke, n (%)	96 (63.6)	92 (59.0)	0.41	56 (60)	63 (68)	0.80
Alcohol, n (%)	60 (39.7)	73 (46.8)	0.21	44 (47)	43 (46)	0.02
Hypertension grade, n (%)			0.78			1.00
I	124 (82.1)	129 (85.4)	–	80 (86.0)	79 (85)	–
II	27 (17.2)	26 (17.2)	–	13 (14.0)	14 (15.0)	–
Pre-existed comorbidity, n (%)						
Coronary artery disease	30 (19.9)	31 (19.9)	1.00	16 (17)	21 (23)	0.56
Diabetes mellitus	31 (19.9)	31 (19.9)	0.83	24 (26)	22 (24)	0.03
Laboratory findings						
Pao ₂ /Fio ₂ ratio, median (interquartile ranges)	112.0 (83.0–160.0)	120.0 (95.0–160.0)	0.83	115.0 (83.0–161.0)	127.0 (95.2–157.6)	1.00
Categories of acute respiratory distress syndrome, n (%)			0.74			0.03
Moderate	98 (64.9)	104 (66.7)	–	65 (70)	63 (68)	–
Severe	53 (35.1)	52 (33.3)	–	28 (30)	30 (32)	–
WBC, median (interquartile ranges)	9.7 (8.2–12.6)	9.5 (6.9–13.5)	0.54	9.7 (8.2–13.3)	9.5 (7.9–13.5)	0.73
Hemoglobin, median (interquartile ranges)	108.0 (89.0–119.0)	114.0 (95.0–131.0)	< 0.01 ^a	107.0 (91.0–120.0)	106.0 (91.0–120.0)	0.97
Platelets, median (interquartile ranges)	130.0 (98.0–193.0)	137.0 (71.0–198.0)	0.6	140.0 (98.0–193.0)	166.0 (114.0–213.0)	0.09
Albumin, median (interquartile ranges)	31.8 (29.0–35.0)	30.1 (26.8–33.3)	< 0.01 ^a	30.8 (27.0–35.0)	30.1 (26.0–33.6)	0.57
Creatinine, median (interquartile ranges)	88.8 (53.0–121.0)	86.0 (60.0–110.5)	0.79	88.8 (54.0–109.0)	91.0 (57.0–123.0)	0.47
Blood urea nitrogen, median (interquartile ranges)	11.7 (8.1–17.0)	11.0 (8.2–17.0)	0.83	12.4 (8.3–17.0)	10.9 (8.1–16.6)	0.13
Lactate dehydrogenase, median (interquartile ranges)	389.0 (278.0–561.0)	302.5 (239.0–491.0)	0.03 ^a	412.0 (288.0–561.0)	306.0 (239.0–491.0)	0.30
Lactate, median (interquartile ranges)	1.9 (1.6–2.9)	2.1 (1.5–2.7)	0.89	2.0 (1.6–2.8)	2.1 (1.5–2.7)	0.66
C-reactive protein, median (interquartile ranges)	103.0 (35.0–151.6)	109.0 (35.0–195.0)	0.42	105.0 (35.0–215.0)	109.0 (35.0–151.6)	0.40
Procalcitonin, median (interquartile ranges)	0.7 (0.3–5.7)	0.9 (0.4–3.3)	0.34	0.8 (0.3–6.4)	0.8 (0.4–2.9)	0.19

(Continued)

TABLE 1. (Continued).**Comparison of Demographics and Clinicopathologic Characteristics of Unmatched and Matched Hospitalized Moderate-Severe Direct Acute Respiratory Distress Syndrome Patients With Hypertension With or Without the Dihydropyridine Calcium Channel Blocker Therapy**

Factors	Pre Matched			Post Matched		
	Without DCCB (N = 151)	With DCCB (N = 156)	p	Without DCCB (N = 93)	With DCCB (N = 93)	p
Acute Physiology and Chronic Health Evaluation II score, median (interquartile ranges)	9.0 (7.0–13.0)	10.0 (7.0–12.0)	0.96	8.0 (6.0–13.0)	9.0 (7.0–12.0)	0.67
Sequential Organ Failure Assessment score, median (interquartile ranges)	2.5 (2.0–4.0)	3.0 (2.0–6.0)	0.03 ^a	2.0 (2.0–4.0)	3.0 (2.0–6.0)	0.05
Outcomes						
Mechanical ventilation, n (%)	115 (76.2)	130 (83.3)	0.12	75 (81)	73 (78)	1.00
Duration of ventilation, median (interquartile ranges)	9.0 2.0–20.0)	11.0 (4.0–17.0)	0.33	9.0 (2.0–20.0)	9.0 (2.0–16.0)	0.40
Shock, n (%)	42 (27.8)	71 (45.5)	< 0.01	31 (33)	42 (45)	0.12
In-hospital mortality, n (%)	61 (40.4)	102 (65.4)	< 0.01	40 (43)	59 (63)	< 0.01
Hospital length of stay, median (interquartile ranges)	18.0 (11.0–26.0)	16.0 (11.0–22.0)	0.07	18.0 (13.0–24.0)	15.0 (10.0–18.0)	0.03

DCCB = dihydropyridine calcium channel blockers.

Dashes indicate that this item is not compared.

^ap < 0.05.

mmol/L (HR, 1.454; 95% CI, 1.041–2.029; $p = 0.028$). Kaplan-Meier analysis showed that in patients without PSM who treated with DCCB had a significant worse mortality (**Fig. 1A**) (log-rank $p < 0.0001$).

Characteristics of Hypertensive Patients With or Without DCCB Was Reported When Moderate-Severe ARDS Induced by Pulmonary Occurred After PSM

In group with PSM, in-hospital mortality was significantly higher in patients treated with DCCB than in those without DCCB (65.4% vs 40.4%; $p < 0.01$). Kaplan-Meier analysis showed that patients not treated with DCCB had a significant survival advantage over those treated with DCCB in patients with PSM (**Fig. 1B**) (log-rank $p = 0.001$).

In this patient population after PSM, the median age was 75.0 years (IQR, 67.0–80.0 yr), and 79.6% (148/186) were male. 46.8% of patients (87/186) had a history of alcohol consumption. The most commonly reported comorbidities were diabetes mellitus, 24.7% (46/186), and coronary artery disease, 19.9% (37/186).

Of the 186 patients, 159 (85.5%) were in hypertension grade I. The proportion of patients with hypertension grade II was 14.5%. In our study, 53.2% of patients (99/186) died during hospitalization. The median length of hospital stay was 16 days (IQR, 12.0–23.0 d) (**Table S1**, <http://links.lww.com/CCX/A749>).

There were no differences in age, history of smoking consumption, hemoglobin, albumin, LDH, or PaO₂/Fio₂ ratio between patients with or without DCCB. Of the 93 patients with a history of chronic DCCB, 79 (85%) were in hypertension grade I, and 14 (15%) were grade II. Among patients treated with DCCB, a lower proportion of patients had the history of alcohol consumption than those who were not treated with DCCB (43 vs 44; $p = 0.02$). Patients treated with DCCB had a larger population of severe ARDS (30 vs 28; $p = 0.03$) and significantly higher SOFA score ($p = 0.05$). However, there was no significant difference in APACHE II score between these two groups ($p = 0.67$). Also, there was no significant difference in mechanical ventilation between DCCB and non-DCCB patients ($p = 1.0$) (**Table 1**).

TABLE 2.**Comparison of Demographics and Clinicopathologic Characteristics of Unmatched and Matched Hospitalized Acute Respiratory Distress Syndrome Patients With Hypertension in Different Prognosis**

Factors	Pre Matched			Post Matched		
	Survivor (N = 144)	Nonsurvivor (N = 163)	p	Survivor (N = 87)	Nonsurvivor (N = 99)	p
Male, %, n (%)	99 (68.8)	137 (84.0)	< 0.01	67 (77)	81 (82)	0.42
Age, median (interquartile ranges)	75.0 (66.0–82.0)	73.0 (66.0–79.0)	0.38	75.0 (67.0–79.0)	75.0 (66.0–83.0)	0.53
Smoke, n (%)	92 (63.9)	96 (58.9)	0.37	56 (64)	63 (64)	0.92
Alcohol, n (%)	58 (40.3)	75 (46.0)	0.31	39 (45)	48 (48)	0.62
With dihydropyridine calcium channel blocker, n (%)	54 (37.5)	102 (62.6)	< 0.01 ^a	34 (39)	59 (60)	< 0.01 ^a
Hypertension grade, n (%)			0.73			0.79
I	118 (81.9)	136 (83.4)	–	75 (86)	84 (85)	–
II	26 (18.1)	27 (16.6)	–	12 (14)	15 (15)	–
Pre-existed comorbidity, n (%)						
Coronary artery disease	33 (22.9)	28 (17.2)	0.21	18 (21)	19 (19)	0.80
Diabetes mellitus	47 (32.6)	34 (20.9)	0.02 ^a	28 (32)	18 (18)	0.03 ^a
Laboratory findings						
Pao ₂ /Fio ₂ ratio, median (interquartile ranges)	120.0 (97.0–166.0)	117.3 (88.0–145.0)	0.04 ^a	115.0 (90.0–161.0)	128.0 (92.0–170.0)	0.87
Categories of acute respiratory distress syndrome, n (%)			0.13			0.72
Moderate	101 (70.1)	101 (62.0)	–	61 (70)	67 (68)	–
Severe	43 (29.9)	62 (38.0)	–	26 (30)	32 (32)	–
WBC, median (interquartile ranges)	9.7 (7.9–13.0)	9.7 (6.9–13.0)	0.72	9.6 (8.0–14.2)	9.7 (8.8–13.0)	0.70
Hemoglobin, median (interquartile ranges)	115.0 (96.0–131.0)	107.0 (91.0–121.0)	0.04 ^a	109.0 (96.0–130.0)	103.0 (89.0–115.0)	< 0.01 ^a
Platelets, median (interquartile ranges)	151.0 (106.0–196.0)	130.0 (67.0–187.0)	< 0.01 ^a	180.0 (109.0–208.0)	136.0 (98.0–198.0)	0.06
Albumin, median (interquartile ranges)	32.1 (30.0–35.0)	30.0 (25.9–34.0)	< 0.01 ^a	32.1 (30.0–35.0)	30.0 (23.6–34.0)	< 0.01 ^a
Creatinine, median (interquartile ranges)	77.0 (60.0–112.0)	91.0 (55.0–121.0)	0.49	86.0 (60.0–123.2)	91.9 (54.0–113.1)	0.95
Blood urea nitrogen, median (interquartile ranges)	11.2 (8.0–16.6)	11.0 (8.4–17.5)	0.05	11.7 (8.0–15.4)	11.0 (8.7–17.5)	0.06
Lactate dehydrogenase, median (interquartile ranges)	308.0 (226.5–419.0)	381.0 (271.0–630.0)	< 0.01 ^a	321.0 (188.8–419.0)	444.0 (280.0–630.0)	< 0.01 ^a
Lactate, median (interquartile ranges)	1.9 (1.3–2.5)	2.2 (1.6–2.9)	0.01 ^a	1.8 (1.2–2.5)	2.1 (1.8–2.8)	0.01 ^a
C-reactive protein, median (interquartile ranges)	105.0 (43.5–175.5)	95.6 (33.6–154.0)	0.22	109.0 (35.0–195.0)	109.0 (35.0–154.0)	0.84
Procalcitonin	0.8 (0.3–2.1)	1.6 (0.3–5.7)	0.02 ^a	0.6 (0.3–1.6)	0.9 (0.3–5.7)	0.04 ^a

(Continued)

TABLE 2. (Continued).

Comparison of Demographics and Clinicopathologic Characteristics of Unmatched and Matched Hospitalized Acute Respiratory Distress Syndrome Patients With Hypertension in Different Prognosis

Factors	Pre Matched			Post Matched		
	Survivor (N = 144)	Nonsurvivor (N = 163)	p	Survivor (N = 87)	Nonsurvivor (N = 99)	p
Acute Physiology and Chronic Health Evaluation II score, median (interquartile ranges)	8.5 (6.0–12.5)	10.0 (7.0–12.0)	0.06	8.0 (6.0–14.0)	9.0 (7.0–12.0)	0.49
Sequential Organ Failure Assessment score, median (interquartile ranges)	3.0 (2.0–4.0)	3.0 (2.0–4.5)	0.47	2.0 (2.0–4.0)	3.0 (2.0–6.0)	0.16
Outcomes						
Mechanical ventilation, n (%)	107 (74.3)	138 (84.7)	0.02 ^a	64 (74)	84 (85)	0.06
Shock, n (%)	36 (25.0)	77 (47.2)	< 0.01 ^a	26 (30)	47 (47)	0.01 ^a
Hospital length of stay, median (interquartile ranges)	18.0 (13.0–24.0)	16.0 (10.0–22.0)	< 0.01 ^a	18.0 (13.0–24.0)	15.0 (10.0–18.0)	< 0.01 ^a

Dashes indicate that this item is not compared.

^ap < 0.05.

By multivariate Cox regression analysis, factors associated with an increased risk of patient death during hospitalization included DCCB (HR, 2.021; 95% CI, 1.333–3.064; $p = 0.001$), LDH greater than or equal to 600 U/L (HR, 4.379; 95% CI, 2.642–7.257; $p < 0.001$), and lactate greater than or equal to 2 mmol/L (HR, 2.461; 95% CI, 1.534–3.951; $p < 0.001$).

DISCUSSION

In this multicenter retrospective survey, DCCB, LDH greater than or equal to 600 U/L, and lactate greater than or equal to 2 mmol/L at admission were

significantly associated with an increased risk of death during hospitalization in hypertensive patients who developed moderate-severe pulmonary ARDS.

Investigation of our group showed that DCCB could induce up-regulation of expression and functional activation of the CaSR in PASM, which leads to the release of calcium from the sarcoplasmic reticulum and facilitates the flow of extracellular calcium, together contributing to an increase in intracellular calcium concentration (24–26). This may lead to increased PASM proliferation, pulmonary vascular permeability, pulmonary fibrosis, and worsen pulmonary hypertension, which could increase mortality in ARDS (27).

TABLE 3.

Multivariate Cox Regression Analysis of Risk Factors for Mortality of Moderate-Severe Direct Acute Respiratory Distress Syndrome Patients With Hypertension

Factors	Pre Matched		Post Matched	
	HR (95% CI)	p	HR (95% CI)	p
With dihydropyridine calcium channel blocker	1.954 (1.415–2.699)	< 0.001	2.021 (1.333–3.064)	0.001
Lactate dehydrogenase ^a ≥ 600	3.089 (2.106–4.531)	< 0.001	4.379 (2.64–7.257)	< 0.001
Lactate ^a ≥ 2 mmol/L	1.454 (1.041–2.029)	0.028	2.461 (1.534–3.951)	< 0.001

HR = hazard ratio.

^aLaboratory finding upon admission.

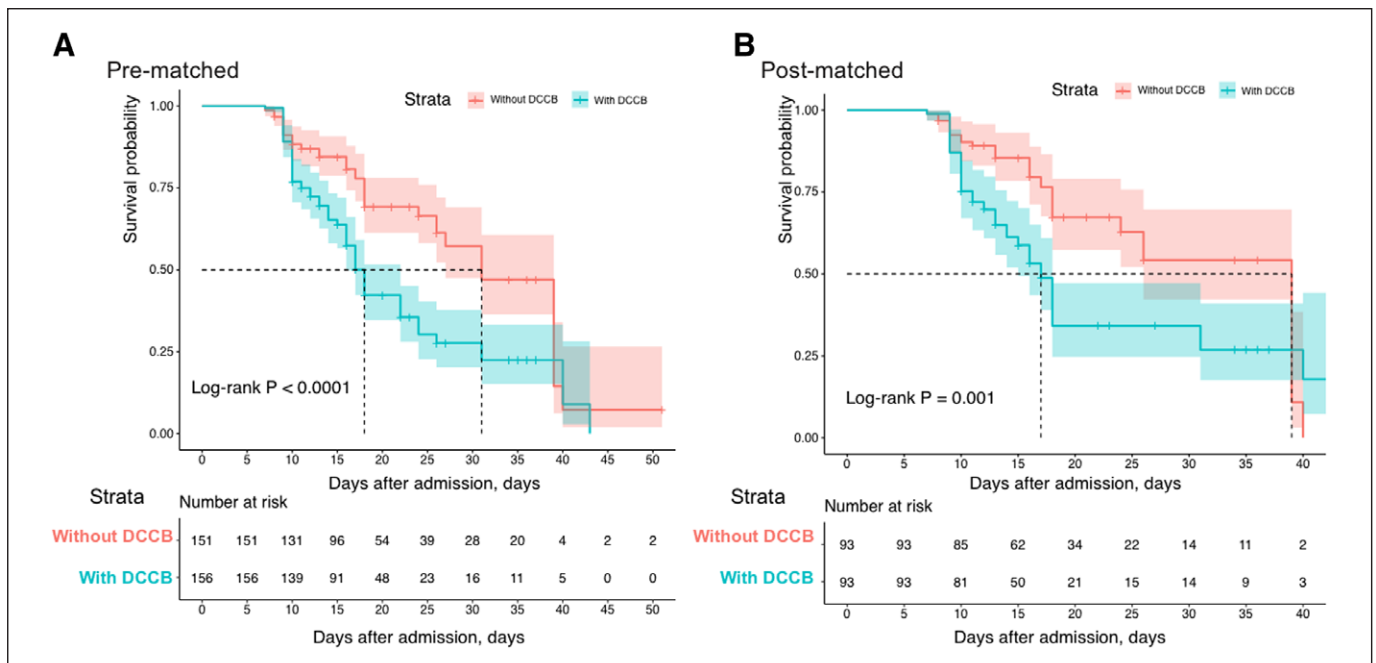


Figure 1. Kaplan-Meier survival curves for mortality during hospitalization. The numbers below the figure represent the number of inpatients at risk of death on a given date who had or did not have the history of dihydropyridine calcium channel blocker (DCCB). **A**, Kaplan-Meier survival curves of mortality for unmatched inpatients. **B**, Kaplan-Meier survival curves of mortality for matched inpatients.

Pulmonary artery endothelial cells migration and proliferation could cause pulmonary vascular obstruction in mitochondrial Ca^{2+} -dependent manner when calcium increases in the cell (26). The increased intracellular Ca^{2+} could induce the apoptosis of type II pneumocytes as well, mediating ARDS-related lung injury (8). These results may explain pulmonary vasoconstriction and reconstitution could improve the mortality rate of patients with pulmonary hypertension in ARDS (6, 12, 28).

Serum lactate has been clinically considered as a marker of tissue hypoxia and is often used as a biological indicator of prognosis (29). Blood lactate is produced by RBCs, brain tissue, and striated muscle. The blood lactate level mainly depends on the synthesis and metabolism speed of the liver and kidneys. Under pathologic conditions, critical illnesses such as respiratory failure or circulatory failure could lead to tissue hypoxia and increased lactate production (30). Thus, the lactic acid level may reflect the severity of the disease to a certain extent. Reports had shown that lung lactate production might become clinically evident in disease states especially in the patients with ARDS (31). Study had also found that lactate has an immunosuppressive effect and played an important role in immune regulation and inflammatory response (32). In our

investigation, we also learned that LDH greater than or equal to 600 U/L is a risk factor for hypertension in patients with ARDS. There were reports showed that higher LDH level could be a predictor of prognosis in patients with ARDS (33, 34). LDH could be released from cells when there was damage to the cytoplasmic membrane. It is not only a metabolic but also an immune surveillance prognostic biomarker (35). LDH could represent an expression of lung damage consequent to the inflammation status. Elevated LDH values have been found in other interstitial lung infections (36).

Some limitations of the present study are worth mentioning. First, this is a retrospective study. Although this multicenter study may be representative, our epidemiology cannot be extrapolated to all settings. PSM could eliminate bias or control confounding, as it may also exacerbate some forms or such forms of bias. In addition, there were many factors that could cause bias that we did not include. Patients' different socioeconomic status might also be a source of deviation. Second, mechanical ventilation strategies are strictly in accordance with the guidelines; there is heterogeneity in organ support therapy due to some patients' lack of invasive hemodynamic monitoring. This may have introduced bias favoring benefit from treatment measures. Finally, pulmonary

arterial hypertension (PAH) World Health Organization (WHO) Group 1 and Group 3 are different diseases and have different pathogenic mechanisms. Our prior works were focused on the PASC from both idiopathic PAH patients and hypoxic pulmonary hypertension (HPH) HPH mice. As the PAH in ARDS patients belongs to WHO Group 3, we make the assumption that CCB may have similar work in HPH mice and in ARDS patients. However, the pathogenesis of ARDS is still unclear; the pathogenesis of ARDS patients with hypertension is much more complex. The mechanism of DCCB affecting the prognosis of patients with hypertension and ARDS needs further study. And, all patients enrolled in the study were given medication for more than 3 months, but the specific duration of medication is still unclear. Our study only provides a clinical clue. Hopefully, our study will provoke some randomized clinical trial researches and basic experiments to further elucidate the effect of DCCB on hypertension combined with ARDS.

CONCLUSIONS

The results of this study provide insight into the effect of DCCB on mortality in patients with hypertension and moderate-severe pulmonary ARDS, with DCCB, LDH greater than or equal to 600 U/L, and lactate greater than or equal to 2 mmol/L at admission being independent risk factors for mortality. Further studies are needed to reveal the effect of DCCB on hypertension combined with moderate-severe pulmonary ARDS.

ACKNOWLEDGMENTS

We thank Lijuan Yang, Ying He, and Feng Yao for their devotion in collecting data. We also thank all staff in medical information department of hospitals for their help in data management.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejjournal>).

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Supported, in part, by Jiangsu Province's Key Provincial Talents Program (ZDRCA2016046) and Key Health Talents in Gusu (GSWS2019009).

The authors have disclosed that they do not have any potential conflicts of interest.

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