Original Article

Clinical characteristics and outcomes of critically ill patients with coronavirus disease 2019 with hypotension in China: a retrospective cohort study

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Background: The characteristics of the coronavirus disease 2019 (COVID-19) patients with hypotension are still limited. We aim to describe the clinical features and outcomes of the patients.

Methods: This was a multicenter retrospective study of critically ill patients with COVID-19 from ICUs in 19 hospitals in China. All patients were followed up to day 28 or death, which came first. Clinical and outcome data were collected and analyzed. Patients were classified as early-onset or late-onset hypotension, and clinical characteristics and outcomes were compared.

Results: A total of 649 patients were included in the final analysis, and 240 (37.0%) were hypotension patients. The median age of hypotension patients was 67 years (IQR, 60–73 years), and 159 (66.2%) were male. 172 (71.7%) of the hypotension patients had at least one comorbidity. The 28-day mortality of the patients with hypotension was 85.4%, which was significantly higher than that of patients without hypotension. Compared with late-onset hypotension patients, the 28-day mortality of patients with early-onset hypotension was significantly higher (90.1% *vs.* 78.6%, P=0.02).

Conclusions: Approximately one third critically ill COVID-19 patients progressed to hypotension. The mortality was significantly higher in hypotension patients than that in patients without hypotension. Compared with patients with late-onset hypotension, the mortality of patients with early-onset hypotension was significantly higher.

Keywords: Critically ill patients; coronavirus disease 2019 (COVID-19); hypotension; clinical features; outcomes

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19) has been initially identified in the Chinese city of Wuhan in December 2019 (1-3). Now, the virus has caused global outbreak and has affected thousands of people so far. A total number of 4,517,399 laboratory-confirmed cases have been documented globally, including 308,515 deaths as of 16 May, 2020 (4). This rapidly evolving situation has created an unprecedented strain on many health care systems, and is an emerging health threat to all mankind.

The severity of the COVID-19 patients appears to vary, including asymptomatic infection, upper respiratory tract illness, pneumonia of different severity, and even death. Although most patients are thought to have a favorable prognosis, the outcome of the patients with severe illness would become significantly worse. Critically ill patients often have systemic involvement of multiple organs and may develop organ dysfunction in the disease course, encompassing acute respiratory distress syndrome (ARDS), hypotension, and acute kidney injury (AKI) (5-7), which is the main cause of poor prognosis. Certain epidemiological, clinical, and pathological features of COVID-19 have been recently reported (8-13). However, the characteristics of COVID-19 patients with hypotension were not well described. In this study, we present details of all critically ill COVID-19 patients with hypotension admitted to 19 hospitals who have experienced a definite outcome in China. We aim to describe the clinical features and outcomes of the patients, and explore risk factors of associated with in-hospital death. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-20-2172).

Methods

Data Sources and study participants

This retrospective cohort study was a second analysis of a previous study which describe the characteristics of critically patients with COVID-19 (14). Patients admitted to one of the ICUs among the 19 hospitals between Jan 1 and Feb 28, 2020, were enrolled. All patients were diagnosed with COVID-19 according to World Health Organization interim guidance. All patients underwent nucleic acid testing by reverse transcription-polymerase chain reaction testing, and the results were positive for COVID-19. This study protocol was approved by each local institutional ethics committee.

Clinical data reported in this study included the followings: age, sex, medical comorbidities, clinical symptoms and signs, laboratory findings on ICU admission, treatment (including antiviral therapy, antibiotics, corticosteroid therapy, immunomodulators, vasoactive drug, continuous renal replacement therapy (CRRT) and respiratory support) during the ICU stay, and Day 28 prognosis in the ICU. Laboratory testing was performed according to the clinical care needs of the patient. Laboratory assessments consisted of a complete blood count, blood gas analysis, coagulation testing, assessment of liver and renal function, Troponin I (TNI), creatine kinase (CK), creatine kinase muscle-brain isoform (CK-MB), C-reactive protein (CRP), and procalcitonin. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Jin Yin-tan Hospital (KY-2020-10.02) and individual consent for this retrospective analysis was waived.

Definitions

Hypotension were defined as mean arterial pressure (MAP) lower than 65 mmHg, not reversed with fluid resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg, and the duration of vasoactive drug use was longer than 24 hours (15). AKI was diagnosed according to the KDIGO clinical practice guidelines and ARDS was diagnosed according to the Berlin Definition (16,17). All the critically ill COVID-19 patients were classified as early-onset hypotension or late-onset hypotension according to the median duration between ICU admission and diagnosis of hypotension. Lymphocytopenia was defined as a lymphocyte count of less than 1,500 cells per cubic millimeter.

Statistical analysis

Continuous variables with non-normal distribution were presented as median and IQR with 95% CIs. Categorical variables were expressed as number of patients (percentage) with 95% CIs. Categorical data were compared using the χ^2 test or the Fisher exact test. Non-normal distribution continuous data were compared using Mann-Whitney-Wilcoxon test. Bivariate Cox proportional hazard ratio (HR) models were used to determine HRs and 95% CIs between

individual factors on the progression from hypotension to death. Survival curves were developed using the Kaplan-Meier method with log-rank test. The analyses regarding different factors were based on nonmissing data and imputed missing data. All tests were 2-sided, and a P value less than 0.05 was considered statistically significant. All analyses were performed with SPSS, version 23.0 (IBM SPSS).

Results

Demographic, epidemiologic, and baseline characteristics

A total of 733 adult critically ill COVID-19 patients were admitted to ICUs in the 19 hospitals between Jan 1 and Feb 28, 2020. Of these patients, 324 (44.2%) were diagnosed as hypotension. After excluding 84 patients who were diagnosed as hypotension within 24 hours of ICU admission, 649 patients were included in the final analysis, including 240 (37.0%) patients with hypotension (*Table 1*). The median duration from symptom onset to hypotension was 18.2 d (IQR, 13–23 d), which is later than the onset of ARDS (Median 8.1 d, IQR, 7–17 d). The median age of the patients with hypotension was 67 years (IQR, 60–73 years), and 159 (66.2%) were male. A total of 172 (71.7%) hypotension patients had at least one comorbidity. The median (IQR) Acute Physiology and Chronic Health Evaluation (APACHE) II score of the patients with hypotension at ICU admission was 13.0 (9.0–16.0), and the median (IQR) Sequential Organ Failure Assessment (SOFA) score was 4.0 (2.0–8.0), both were significantly higher than the values of the patients without hypotension.

Clinical characteristics, laboratory findings, and main treatments

The most common symptoms of the patients with hypotension at onset were fever (206 patients, 85.8%) and cough (180 patients, 75.0%; *Table 1*). Compared with patients without hypotension, shortness of breath and fatigue were more common among patients with hypotension. Heart rate and respiratory rate on admission were both higher among patients with hypotension than patients without hypotension [96.0 (81.0–108.0) *vs.* 89.0 (80.0–100.0), P=0.01; 26.0 (21.0–32.0) *vs.* 22.0 (20.0–26.0), P=0.00]. There were many differences in laboratory findings on ICU admission between patients with hypotension and those without hypotension, including higher white blood cell, lower lymphocyte and PaO_2/FiO_2, as well as higher levels of total bilirubin, LDH, D-dimer, prothrombin time, creatinine, TNI, CK-MB, CRP, and procalcitonin (*Table 1*).

During ICU stay, 177 (73.8%) patients with hypotension received antiviral therapy. Systemic glucocorticoids were given to 148 patients (61.7%), and more than half of patients received immunomodulators. There was no difference in above drug interventions between patients with hypotension and without hypotension. Of the 240 patients with hypotension, 231 patients (96.2%) progressed to ARDS. Although high-flow nasal cannula (HFNC) oxygen therapy was administered in 161 patients with hypotension (67.1%) and noninvasive mechanical ventilation in 158 (65.8%), invasive mechanical ventilation was required in 201 (83.8%) patients with hypotension. As of the 201 intubated patients, 169 (70.4%) patients were intubated within 48 h of the diagnosis of hypotension. At ICU admission, AKI developed in 71 patients (29.6%), and aspartate aminotransferase or alanine aminotransferase greater than 40 U/L developed in 135 patients (56.2%). More patients with hypotension received CRRT than patients without hypotension [64 (26.7%) *vs.* 15 (3.7%), P=0.00; *Table 1*].

Clinical outcomes

As of 28 days after ICU admission, of the 240 critically ill COVID-19 patients with hypotension, 205 patients died, 16 have discharged from hospital, and 19 were still in hospital. The mortality of patients with hypotension was significantly higher than that of patients without hypotension (85.4% *vs.* 30.3%, P=0.00; *Table 1*, *Figure 1*).

Compared with survivors of patients with hypotension, nonsurvivors were older and had higher APACHE II and lower PaO_2/FiO_2 ratio at admission to ICU. For patients with hypotension who died, the value of LDH, C-reactive protein, D-dimer, and creatinine were significantly elevated compared with patients with hypotension who survived. For survivors, more patients were tested negative for the virus during treatment than non-survivors (34.3% *vs.* 7.8%, P=0.00; Table S1). The risk of COVID-19 nucleic acid positivity was 2.1 times higher in patients who died than those who survived (Figure S1). Mortality was significantly higher in patients who were treated with HFNC or noninvasive mechanical ventilation first than those were treated with intubation first (*Figure 2*). Compared with patients who initiated invasive mechanical ventilation more than 48 h before hypotension diagnosis, more patients died when the invasive mechanical ventilation initiated within 48 h of hypotension diagnose. When considering

Table 1 Demographics and clinical characteristics of critically ill COVID-19 patients with hypotension

Characteristic	All patients (n=649)	Hypotension (n=240)	Non-hypotension (n=409)	P Value
Demographics characteristics				
Age, median (IQR), yr	65.0 (56.0–72.0)	67.0 (60.0–73.0)	63.0 (54.0–71.0)	0.00
Age ≤60, n (%)	236 (36.4)	68 (28.3)	168 (41.0)	0.01
Age >60, n (%)	413 (63.6)	172 (71.7)	241 (58.9)	
Male sex, n (%)	427 (65.8)	159 (66.2)	268 (65.2)	0.85
Comorbidities, n (%)				
Hypertension	268 (41.3)	166 (69.2)	102 (24.9)	0.00
Chronic heart disease	84 (12.9)	35 (14.6)	49 (12.0)	0.00
Diabetes	121 (18.6)	54 (22.5)	67 (16.4)	0.30
COPD	33 (5.1)	15 (6.3)	18 (4.4)	0.30
Chronic renal insufficiency	12 (1.8)	9 (3.8)	3 (7.5)	0.30
Solid malignancy	19 (2.9)	8 (3.3)	11 (2.7)	0.64
Severity and time of hypotension (IQR)				
APACHE II score on ICU admission	10.0 (7.0–14.0)	13.0 (9.0–16.0)	9.0 (5.0–12.0)	0.00
SOFA score on ICU admission	3.0 (1.0–5.0)	4.0 (2.0–8.0)	3.0 (0.5–4.0)	0.04
Median time between ICU admission and hypotension, d	–	7.0 (3.0–13.0)	–	–
Symptoms on admission, n (%)				
Fever	555 (85.5)	206 (85.8)	349 (85.3)	0.86
Cough	490 (75.5)	180 (75.0)	313 (75.8)	0.82
Shortness of breath	381 (58.8)	173 (72.1)	208 (50.9)	0.00
Diarrhea	82 (12.6)	33 (13.8)	49 (12.0)	0.51
Fatigue	353 (54.4)	156 (65.0)	156 (65.0)	0.00
Vital sign on admission (IQR)				
Temperature (degrees centigrade)	36.7 (36.5–37.6)	36.8 (36.5–37.3)	36.8 (36.5–37.8）	0.58
Heart rate (beats/min)	90.0 (81.0–103.0)	96.0 (81.0–108.0)	89.0 (80.0–100.0)	0.01
Respiratory rate (beats/min)	23.0 (20.0–28.0)	26.0 (21.0–32.0)	22.0 (20.0–26.0)	0.00
Mean arterial pressure (mmHg)	95.0 (87.0–103.0)	95.0 (83.0–103.0)	95.0 (88.0–103.0)	0.35
Laboratory data on ICU admission (IQR)				
PaO_2/FiO_2 (mmHg)	111.8 (61.4–246.8)	86.5 (52.0–153.4)	141.9 (70.2–315.6)	0.00
Leukocyte count ($\times10^9$/L)	9.0 (5.5–12.8)	10.4 (7.9–14.8)	7.5 (4.9–12.0)	0.00
Lymphocyte count ($\times10^9$/L)	0.6 (0.4–0.9)	0.5 (0.3–0.8)	0.7 (0.5–1.0)	0.00
Platelet ($\times10^9$/L)	169.0 (122.0–223.0)	169.0 (116.8–225.0)	168.5 (124.3–215.8)	0.78
Total bilirubin (μmol/L)	12.8 (9.2–19.1)	13.7 (9.9–21.4)	12.0 (8.6–17.5)	0.00
Lactate dehydrogenase (U/L)	462.0 (319.0–628.0)	543.0 (402.0–812.0)	426.0 (282.0–586.6)	0.00

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	All patients (n=649)	Hypotension (n=240)	Non-hypotension (n=409)	P Value
Alanine aminotransferase (U/L)	33.0 (21.0–53.0)	33.5 (21.1–51.0)	38.0 (27.3–63.8)	0.67
Aspartate aminotransferase (U/L)	37.0 (27.0–59.0)	38.0 (27.3–63.8)	38.0 (26.0–56.0)	0.55
Albumin (g/L)	30.5 (27.1–35.2)	29.5 (26.5–32.4)	32.0 (27.6–38.0)	0.00
C-reactive protein (mg/L)	75.2 (31.0–139.6)	82.7 (43.5–150.9)	68.5 (23.5–126.0)	0.00
Procalcitonin (ng/mL)	0.2 (0.1–1.3)	0.3 (0.1–0.9)	0.3 (0.1–2.1)	0.00
Prothrombin time (s)	13.3 (11.9–15.1)	14.2 (12.2–15.7)	13.0 (11.9–14.6)	0.00
Activated partial thromboplastin time (s)	33.8 (27.4–40.1)	33.8 (27.4–40.2)	33.9 (27.5–40.1)	0.89
International normalized ratio	1.1 (1.0–1.2)	1.1 (1.0–1.3)	1.0 (1.0–1.2)	0.00
D-dimer (ug/L)	2.6 (0.7–8.0)	5.3 (1.3–17.4)	1.5 (0.5–7.2)	0.00
Serum urea (mmol/L)	6.9 (4.9–10.2)	7.8 (5.6–11.2)	6.3 (4.6–9.6)	0.00
Creatinine (μmol/L)	71.0 (56.9–94.0)	72.4 (57.0–94.4)	70.0 (57.0–94.0)	0.58
Troponin I (ng/mL)	24.6 (10.0–90.5)	30.0 (10.6–138.9)	15.3 (9.0–58.3)	0.00
Creatine kinase (ng/mL)	89.9 (49.9–205.0)	98.0 (49.8–246.5)	85.0 (49.0–183.0)	0.29
Creatine kinase MB isoenzyme (ng/mL)	12.7 (2.6–20.0)	14.0 (5.8–21.3)	12.0 (1.50–19.0)	0.00
Therapy, and outcome				
Antiviral therapy, n (%)	501 (77.2)	177 (73.8)	324 (79.2)	0.05
Glucocorticoid therapy, n (%)	407 (62.8)	148 (61.7)	259 (63.3)	0.46
IV immunoglobulin therapy, n (%)	342 (52.7)	215 (52.8)	126 (52.5)	0.74
HFNC, n (%)	388 (59.8)	161 (67.1）	183 (44.7)	0.00
NIV, n (%)	338 (52.1)	158 (65.8)	177 (43.3)	0.00
IMV, n (%)	253 (39.0)	201 (83.8)	52 (12.7)	0.00
CRRT, n (%)	79 (12.2)	64 (26.7)	15 (3.7)	0.00
Virus shedding, n (%)*	214 (33.0)	28 (11.7)	186 (45.5)	0.00
Median time of positive nucleic acid, (IQR), d	24.0 (17.0–33.0)	28.5 (19.0–39.3)	23.0 (17.0–30.0)	0.00
ICU length of stay, (IQR), d	10.0 (5.0–19.0)	8.0 (5.0–14.0)	12.0 (5.0–23.0)	0.00
Hospital length of stay, (IQR), d	15.0 (9.0–24.0)	12.0 (8.0–21.0)	17.0 (11.0–26.5)	0.00
ICU mortality at 28 d, n (%)	329 (50.7)	205 (85.4)	124 (30.3)	0.00

*, all patients (n=291), Hypotension (n=73), Without hypotension (n=218). COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inhalation oxygen; HFNC, high-flow nasal cannula; NIV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy.

prognostic factors of the critically ill COVID-19 patients with hypotension, bivariate cox models showed that higher APACHE II score, lower PaO_2/FiO_2, elevated D-dimer and HFNC and noninvasive mechanical ventilation were associated with increased HR of death (*Table 2*).

Compared patients with early-onset hypotension with patients with late-onset hypotension

The median duration from ICU admission to diagnosis of hypotension was 7 d (IQR, 3.0–13.0 d), according to the time duration, 142 cases of the 240 critically ill COVID-19

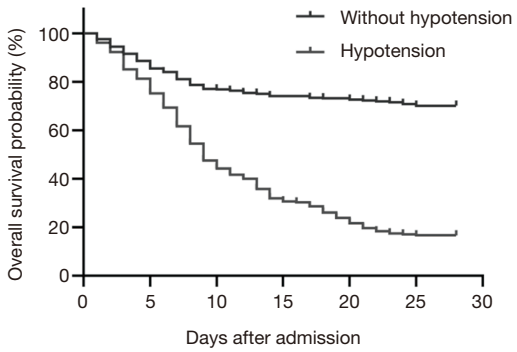

Figure 1 Survival curve in patients hospitalized with critically ill COVID-19 with and without hypotension.

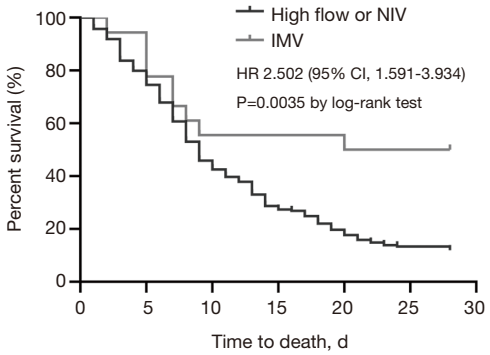

Figure 2 Survival curve in critically ill COVID-19 hypotension patients with different respiratory support. NIV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation.

Table 2 Bivariate cox regression of factors associated with in-hospital death in critically ill COVID-19 patients with hypotension

Factor	Univariate analysis			Multivariate analysis		
	P	Hazard ratio	95% confidence interval	P	Hazard ratio	95% confidence interval
Age	0.002	1.731	1.227–2.444	0.200	1.271	0.881–1.835
APACHE II	0.000	1.951	1.398–2.723	0.006	1.649	1.153–2.358
PaO_2/FiO_2	0.000	1.352	1.028–1.635	0.008	1.323	1.102–1.537
Lymphocyte	0.660	0.940	0.715–1.236	0.265	1.182	0.881–1.548
AST	0.601	1.078	0.814–1.426	0.223	0.829	0.613–1.121
Platelet	0.091	0.789	0.600–1.039	0.815	0.965	0.717–1.299
D-dimer	0.008	1.667	1.141–2.435	0.040	1.544	1.020–2.336
CKMB	0.015	1.513	1.083–2.115	0.307	1.214	0.837–1.762
PCT	0.003	1.533	1.158–2.030	0.417	1.138	0.833–1.556
HFNC or NIV	0.050	1.324	1.000–1.726	0.013	1.450	1.082–1.942
Nucleic acid	0.008	1.257	1.061–1.489	0.112	1.165	0.965–1.407

APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; CKMB, creatine kinase MB isoenzyme; PCT, procalcitonin; HFNC, high-flow nasal cannula; NIV, noninvasive mechanical ventilation.

patients with hypotension were classified as early-onset hypotension and 98 cases as late-onset hypotension (*Table 3*). The median (IQR) APACHE II score and the median (IQR) SOFA score on ICU admission did not differ between the two groups. PaO_2/FiO_2 on ICU admission was significantly lower among patients with early-onset hypotension than patients with late-onset hypotension [82.9 (52.6–118.9) *vs.* 109.1 (62.8–190.4), P=0.03]. The median (IQR) LDH of the patients with early-onset hypotension on ICU admission was significantly higher than the values of the patients with late-onset hypotension [625.0 (432.0–870.5) *vs.* 462.0 (367.5–643.8), P=0.00], so did TNI, CK and CK-MB. Compared with patients with late-onset hypotension, the ICU mortality of patients with early-onset hypotension at 28 day was significantly higher (90.1% *vs.* 78.6%, P=0.02; *Table 3*).

Discussion

Data on critically ill COVID-19 patients with hypotension is scare. In this study, we reported the clinical characteristics and risk factors associated with clinical outcomes in

Table 3 Demographics and clinical characteristics of critically ill COVID-19 patients with hypotension according to the time at risk

Characteristic	Early-onset hypotension (n=142)	Late-onset hypotension (n=98)	P value
Demographics characteristics			
Age, median (IQR), yr	66.8 (56.0–75.0)	62.5 (55.0–73.0)	0.28
Male sex, n (%)	99 (69.7)	61 (62.2)	0.21
Comorbidities, n (%)			
Hypertension	69 (48.6)	48 (50.0)	0.80
Chronic heart disease	21 (14.8)	13 (13.3)	0.72
Diabetes	31 (21.8)	23 (23.5)	0.45
Severity (IQR)			
APACHE II score on ICU admission	12.0 (9.0–18.0)	11.0 (8.0–16.0)	0.43
SOFA score on ICU admission	5.0 (3.0–7.0)	4.0 (3.0–6.0)	0.06
Symptoms on admission, n (%)			
Fever	126 (88.7)	82 (83.7)	0.06
Cough	105 (73.9)	73 (74.5)	0.76
Shortness of breath	109 (76.8)	65 (66.3)	0.05
Diarrhea	24 (16.9)	12 (12.2)	0.36
Fatigue	80 (56.3)	64 (65.3)	0.08
Laboratory data on ICU admission (IQR)			
PaO_2/FiO_2 (mmHg)	82.9 (52.6–118.9)	109.1 (62.8–190.4)	0.03
Leukocyte count ($\times10^9$/L)	12.6 (8.0–17.5)	11.6 (8.3–17.0)	0.78
Lymphocyte count ($\times10^9$/L)	0.5 (0.4–0.8)	0.6 (0.3–0.8)	0.41
Lactate dehydrogenase (U/L)	625.0 (432.0–870.5)	462.0 (367.5–643.8)	0.00
C-reactive protein (mg/L)	112.9 (44.3–162.5)	87.9 (51.8–159.7)	0.83
Procalcitonin (ng/mL)	0.4 (0.2–1.4)	0.3 (0.1–1.0)	0.20
Troponin I (ng/mL)	102.9 (55.2–581.3)	35.6 (13.2–148.9)	0.02
Creatine kinase (ng/mL)	126.7 (55.3–386.4)	73.5 (48.0–162.6)	0.02
Creatine kinase MB isoenzyme (ng/mL)	15.1 (8.3–18.4)	11.3 (6.4–13.8)	0.01
Therapy, and outcome			
Antivirus Drug, n (%)	105 (73.9)	69 (70.4)	0.43
Glucocorticoid, n (%)	93 (65.5)	56 (57.1)	0.62
IMV, n (%)	130 (91.5)	88 (89.8)	0.82
Virus Shedding, n (%)*	23 (51.1)	20 (60.6)	0.53
Median time of positive nucleic acid, (IQR), d	23 (18.0–43.0)	33.0 (22.0–42.0)	0.07
ICU length of stay, (IQR), d	9.0 (6.0–15.0)	13.0 (7.0–20.0)	0.08
Hospital length of stay, (IQR), d	12.0 (9.5–19.0)	20.0 (12.0–28.0)	0.00
ICU mortality at 28 d, n (%)	128 (90.1)	77 (78.6)	0.02

*, early-onset hypotension (n=45), late-onset hypotension (n=33). APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inhalation oxygen; IMV, invasive mechanical ventilation.

critically ill COVID-19 patients with hypotension. Data of the research was obtained from 649 patients with complete clinical course and established clinical outcomes. The results showed that approximately one third critically ill COVID-19 patients progressed to hypotension. More than three quarters of the patients with hypotension died at day 28. The mortality was significantly higher in hypotension patients than that in patients without hypotension. Compared with patients with late-onset hypotension, the mortality of patients with early-onset hypotension was significantly higher. In addition, APACHE II score, lower PaO_2/FiO_2, elevated D-dimer, and HFNC and noninvasive mechanical ventilation were associated with increased HR of death.

Current studies showed, in accordance with other critically ill patients, COVID-19 patients often have systemic involvement of multiple organs during the disease course (18-20). Our results showed that approximately one third of the critically ill COVID-19 patients progressed to hypotension during the course of the disease. Previous researches reported cardiac complications are common in patients with pneumonia (21,22). In the study, TNI increased in patients with hypotension and was higher than that in patients without hypotension, more than half of those with TNI increased died. Therefore, we speculate the potential myocardial injury may be one of the causes of hypotension. In addition, it is widely recognized that critically ill patients are susceptible to infections through various mechanisms, such as immunosuppression and mechanical ventilation (23). Secondary infections may be also an important cause of hypotension.

APACHE II score is a good severity marker for critically ill patients, and reflects the state and degree of multi-organ dysfunction. Current reports determined that critically ill COVID-19 patients often have respiratory system, the heart, kidney, liver, and coagulation system disorder during the disease course. our result was in accordance with previous studies about organ dysfunction, in which ARDS is the most common complication (24-26), and often followed by myocardial dysfunction and hypotension, and AKI. Sometimes multiple system involvement was observed even at the time of initial hospital admission, potentially leading to poor outcome. Therefore, APACHE II score was helpful in predicting hospital mortality in critically ill COVID-19 patients with hypotension (27).

Increased D-dimer indicates abnormal coagulation function. Viral infection and hypotension can activate coagulation cascade through various mechanisms, such as excessive inflammation, hypoxia (5,7,19), leading to severe hypercoagulability and may predispose to thromboembolis, which may be one of the causes of morbidity and mortality death in COVID-19 patients with hypotension. A recent study showed 31% incidence of thrombotic complications in ICU patients with COVID-19 infections, of which CTPA and/or ultrasonography confirmed VTE in 27% and arterial thrombotic events in 3.7% (28). In view of this, monitoring and timely treatment towards coagulation abnormal may thereby reduce the risk of death of COVID-19 patients with hypotension.

The imbalance between oxygen supply and demand is the critical pathophysiological mechanism of hypotension. Shortness of breath and ARDS, the common symptom and complication of critically ill COVID-19 patients with hypotension, exacerbates the imbalance. So, proper respiratory support is not only an important treatment to correct hypoxia, but also a key treatment strategy for hypotension. Our result indicated HFNC and noninvasive mechanical ventilation was associated with increased HR of death. It is consistent with previous study that showed HFNC and noninvasive mechanical ventilation may be insufficient to manage ARDS (24,29,30). More importantly, more patients in our studies died when invasive mechanical ventilation initiated late to within 48 h of hypotension diagnosis, indicating delayed intubation for COVID-19 patients with hypotension was associated with increased mortality. Therefore, it is especially critical to avoid delaying intubation and mechanical ventilation for any reason for critically ill COVID-19 patients with hypotension.

The duration of infectious virus replication affects not only decision making but also the patients condition. In the research, we found that the detectable SARS-CoV-2 RNA persisted for a median of 31 days in COVID-19 patients with hypotension, and sustained viral detection in samples was observed in both survivors and non-survivors. This is similar to MERS-CoV RNA detection in lower respiratory specimens which persisted positive for at least 3 weeks (31). Our results also showed that the risk of COVID-19 nucleic acid positivity was 2.1 times higher in patients who died than those who survived, indicating patients with SARS-CoV-2 prolonged positive was more likely to have poor outcome, which is consistent with the severe influenza virus infection (32). Exploring effective immune regulation and antiviral treatment to promote virus clearance might improve outcomes in critically ill COVID-19 patients with hypotension.

There were differences in clinical characteristics and outcome between patients with early-onset hypotension and those with late-onset hypotension, which suggest there may be the difference of reason and pathophysiology between early-onset hypotension and late-onset hypotension. Evidence from a report showed that east respiratory syndrome (MERS)-CoV causes acute myocarditis (33), and a recent report on 138 COVID-19 patients showed that 7.2% of the patients developed acute cardiac injury, and critically ill patients were more likely to have cardiac injury (7). Our analysis indicated LDH, TNI, CK and CK-MB of the patients with early-onset hypotension on admission were all significantly higher than the values of the patients with late-onset hypotension. Thus, it is rational to hypothesize that early-onset hypotension might be mediated mainly by acute cardiac injury. However, the late-onset hypotension may be caused by other causes, such as secondary infection.

Our study has some limitations. First, for the retrospective study design, not all detailed data were acquired. Second, the critical state of the pandemic outbreak did not allow to performed hemodynamic monitoring. Third, there could well have been many patients who did not come to ICU for the limitations on medical resources and would have been missed. Last but not least, interpretation of our findings might be limited by missing data for some outcomes.

Conclusions

In this retrospective observational study of critically ill COVID-19 patients admitted to ICUs who have experienced a definite outcome, approximately nearly one third patients progressed to hypotension. More than three quarters of the patients with hypotension died at day 28. The mortality was significantly higher than that in patients without hypotension. Compared with patients with late-onset hypotension, the 28-day mortality of patients with early-onset hypotension was significantly higher. Higher APACHE II score, lower PaO_2/FiO_2, elevated D-dimer, and HFNC and noninvasive mechanical ventilation were risk factors for death of critically ill COVID-19 patients with hypotension.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-20-2172). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Jin Yin-tan Hospital (KY-2020-10.02) and individual consent for this retrospective analysis was waived.

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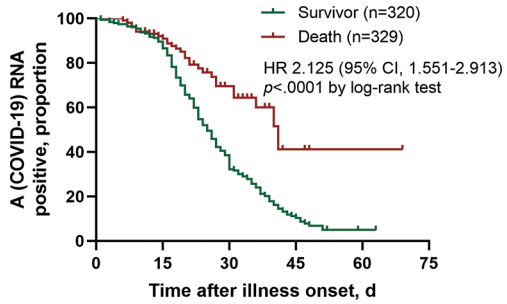

Figure S1 Virus shedding in hospitalized critically ill COVID-19 patients with hypotension who survived and died.

Table S1 Demographics and clinical characteristics of survivor and non-survivor

Characteristic	All hypotension patients (n=240)	Non-survivor (n=205)	Survivor (n=35)	P Value
Demographics characteristics				
Age, median (IQR), yr	67.0 (60.0–73.5)	68.0 (62.0–75.0)	57.0 (50.0–69.0)	0.00
Age ≤60, n (%)	68 (28.3)	43 (21.0)	25 (71.4)	0.00
Age >60, n (%)	172 (71.7)	162 (79.0)	10 (28.6)	
Male sex, n (%)	159 (66.2)	135 (65.9)	46 (68.6)	0.75
Comorbidities, n (%)				
Hypertension	166 (69.2)	155 (75.6)	12 (34.3)	0.00
Chronic heart disease	35 (14.6)	31 (15.1)	4 (11.4)	0.57
Diabetes	54 (22.5)	42 (20.5)	12 (34.3)	0.07
COPD	15 (6.3)	13 (6.3)	2 (5.7)	0.89
Chronic renal insufficiency	9 (3.8)	7 (3.4)	2 (5.7)	0.51
Solid malignancy	8 (3.3)	7 (3.4)	1 (3.0)	0.87
Severity and time of hypotension (IQR)				
APACHE II score on ICU admission	13.0 (9.0–17.0)	13.0 (10.0–17.0)	10.0 (8.0–14.0)	0.00
SOFA score on ICU admission	5.0 (3.0–9.0)	5.0 (3.0–9.0)	3.0 (2.0–6.0)	0.00
Symptoms on admission, n (%)				
Fever	206 (85.8)	177 (86.3)	29 (82.0)	0.59
Cough	180 (75.0)	152 (74.1)	28 (80.0)	0.46
Shortness of breath	173 (72.1)	149 (72.7)	24 (68.6)	0.62
Diarrhea	33 (13.8)	25 (12.2)	8 (22.9)	0.09
Fatigue	156 (65.0)	136 (66.3)	20 (57.1)	0.29
Vital sign on admission (IQR)				
Temperature (degrees centigrade)	36.6 (36.5–37.3)	36.7 (36.5–37.5)	36.6 (36.2–37.9)	0.96
Heart rate (beats/min)	96.0 (82.0–108.0)	96.0 (82.0–108.0)	100.0 (80.0–117.0)	0.67
Respiratory rate (beats/min)	26.0 (21.0–32.0)	26.0 (22.0–32.0)	24.0 (20.0–28.0)	0.04
Mean arterial pressure (mmHg)	95.5 (83.3–103.7)	96.3 (83.0–105.0)	92.7 (83.8–100.3)	0.29

Table S1 (*continued*)

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Table S1 (*continued*)

Characteristic	All hypotension patients (n=240)	Non-survivor (n=205)	Survivor (n=35)	P Value
Laboratory data on ICU admission (IQR)				
PaO_2/FiO_2 (mmHg)	86.6 (57.5–156.2)	83.1 (52.4–130.2)	118.5 (83.4–228.0)	0.00
Leukocyte count ($\times10^9$/L)	10.4 (7.9–14.8)	10.4 (7.9–14.8)	10.0 (7.4–15.5)	0.95
Lymphocyte count ($\times10^9$/L)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.19
Platelet ($\times10^9$/L)	169.0 (116.8–235.0)	168.0 (114.5–233.5)	185.0 (136.5–246.5)	0.17
Lactate dehydrogenase (U/L)	543.0 (402.0–812.0)	570.5 (422.8–831.3)	417.0 (295.0–624.5)	0.00
Alanine aminotransferase (U/L)	33.50 (21.1–51.0)	33.0 (21.0–54.5)	34.0 (23.0–64.0)	0.77
Aspartate aminotransferase (U/L)	38.0 (27.3–63.8)	39.0 (28.0–64.5)	31.0 (22.0–57.0)	0.16
C-reactive protein (mg/L)	82.7 (43.5–150.9)	86.0 (45.7–156.3)	62.2 (24.4–90.3)	0.01
Procalcitonin (ng/mL)	0.3 (0.1–0.9)	0.3 (0.1–1.0)	0.2 (0.1–0.5)	0.63
Prothrombin time (s)	14.2 (12.2–15.7)	14.2 (12.2–15.9)	14.1 (12.1–15.2)	0.72
D-dimer (ug/L)	5.2 (1.3–17.4)	5.6 (1.3–18.6)	2.5 (1.2–8.0)	0.05
Creatinine (μmoL/L)	72.4 (57.0–94.4)	74.0 (60.0–99.2)	61.5 (46.4–75.2)	0.00
Troponin I (ng/mL)	30.0 (10.6–138.9)	30.0 (10.2–155.0)	30.0 (13.4–93.8)	0.88
Creatine kinase (ng/mL)	98.0 (49.8–246.5)	102.0 (52.0–273.0)	65.4 (38.0–132.0)	0.03
Therapy, and outcome				
Antiviral therapy, n (%)	177 (73.8)	150 (73.2)	27 (77.1)	0.62
Glucocorticoid therapy, n (%)	148 (61.7)	129 (62.9)	19 (54.3)	0.33
IV immunoglobulin therapy, n (%)	215 (52.8)	103 (50.2)	23 (65.7)	0.09
IMV, n (%)	201 (80.3)	172 (83.9)	29 (82.9)	0.88
Initiated within 48h of hypotension	169 (70.4)	158 (77.1)	11 (31.4)	0.03
Initiated earlier more than 48h of hypotension	32 (13.3)	18 (8.8)	14 (40.0)	
Intubation after HFNC + NIV	181 (90.0)	163 (79.5)	18 (51.4)	0.02
Direct intubation	20 (8.3)	12 (5.9)	8 (22.9)	
CRRT, n (%)	64 (26.7)	56 (27.3)	8 (22.9)	0.58
Virus Shedding, n (%)*	28 (11.7)	16 (7.8)	12 (34.3)	0.00
ICU length of stay, (IQR), d	8.0 (5.0–14.0)	8.0 (5.0–13.0)	33.0 (27.3–40.5)	0.00
Hospital length of stay, (IQR), d	12.0 (8.0–21.0)	11.0 (7.0–18.5)	33.0 (27.3–40.5)	0.00

*, All shock patients (n=73), Non-survivor (n=34), Survivor (n=39). COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inhalation oxygen; HFNC, high-flow nasal cannula; NIV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy.

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