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Predictors of mechanical ventilation for COVID-19: combined data from three designated hospitals

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Abstract. – OBJECTIVE: Whether patients with COVID-19 require invasive mechanical ventilation (MV) is not yet clear. This article summarizes the clinical treatment process and clinical data of patients with COVID-19 and analyzes the predictive factors for mechanical ventilation for these patients.

MATERIALS AND METHODS: A retrospective study was carried out from January 5, 2020, to March 23, 2020, including 98 patients with COVID-19 treated at three designated hospitals in Huangshi City, Hubei Province. Data collection included demographics, previous underlying diseases, clinical manifestations, laboratory examinations, imaging examination results, diagnosis, and prognosis. This study presents a summary of the patients' overall clinical characteristics and clarifies the predictive factors for MV in patients with COVID-19.

RESULTS: There were 56 males and 42 females included in this study. The mortality rate was 26.53% (26/98). Fever, cough, and chest tightness were the most common symptoms (64.3%, 37.8%, and 12.2%, respectively). Thirty cases required MV, 30.61% of the total cases, and the mortality rate was 73.33%. The univariate comparison showed that dyspnea, acute physiologic assessment, chronic health evaluation (APACHE II) score, and the ratio between arterial blood oxygen partial pressure (PaO_2) and oxygen concentration (FiO_2) (P/F) were statistically different between the MV group and the non-MV group ($p < 0.05$).

CONCLUSIONS: Results showed the following: dyspnea; increased white blood cell count; decreased platelets; lowered albumin levels; increased urea nitrogen; increased levels of myocardial enzymes Creatine Kinase (CK), Creatine Kinase, MB Form (CKMB) and lactate dehydrogenase (LDH); increased lactate, and lowered blood calcium tests. These findings may indicate that the patients have an increased probability of needing MV support. A cutoff value for the initial APACHE II score of >11.5 and the initial PaO_2/FiO_2 ratio of <122.17 mmHg should be considered for MV support for patients with COVID-19.

Key Words:
COVID-19, Mechanical ventilation, Albumin, APACHE II score, PaO_2/FiO_2 ratio.

Introduction

The new coronavirus infection (COVID-19) has escalated into a pandemic since the end of 2019 and spread rapidly. The infection rate is high, the condition varies greatly, the complications are complex and changeable, and the clinical symptoms are diverse. Severe and critical cases continue to emerge, and many critically ill patients require invasive mechanical ventilation (MV) to give them the best chance of survival. High demand resulted in a shortage of ventilators in some areas and high mortality of these patients. This has become a serious challenge for medical personnel in countries across the world[1]. In this study, we analyze the clinical symptoms, morbidity characteristics, medical history, and laboratory tests of patients with COVID-19 and attempt to discover the early factors that predict the need for

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MV. Finally, we evaluate its role in the treatment of COVID-19.

Materials and Methods

Data Collection

In this study, data from patients over the age of 30 who had COVID-19 infection in three designated hospitals were collected retrospectively. The medical charts of all eligible patients between January 5, 2020, and March 23, 2020, were reviewed. All cases were sent to the Huangshi City Center for Disease Control and Prevention, and COVID-19 infection was diagnosed using the nucleic acid detection by nasal swab Reverse Transcription-Polymerase Chain Reaction (RT-PCR) method. The diagnostic criteria of COVID-19 followed the "New Coronavirus Infected Pneumonia Diagnosis and Treatment Program (Seventh Edition)" of the National Health Commission[2]. They were graded according to their clinical classification, as follows:

1. Mild, with mild clinical symptoms, no radiological manifestations of pneumonia.
2. Ordinary, with fever, respiratory tract infection and other symptoms, and pneumonia detectable on radiography.
3. Severe, with (1) shortness of breath, respiratory rate (RR) >30 times/min; (2) resting oxygen saturation ≤93%; (3) Arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) (P/F) ≤300 mmHg (1 mmHg = 0.133 kPa) (at high altitude, over 1000 meters above sea level, P/F should be corrected according to the following formula: $PaO_2/FiO_2 \times$ [atmospheric pressure (mmHg)/760]. Pulmonary imaging showed that the lesions progressed significantly, >50%, within 24-48 hours and these were managed according to severity.
4. Critical, with one of the following conditions: (1) respiratory failure requiring MV; (2) shock; (3) other organ failure requiring intensive care management.

The exclusion criteria for this study were patients who (1) were younger than 18; (2) had incomplete clinical data, which would affect the quality of the analysis; or (3) had an uncertain prognosis due to transfer to another hospital.

The following information was obtained from the medical records of each patient: gender, age, main complaint, clinical symptoms and signs (such as fever, cough, weakness, chest distress, dyspnea, diarrhea or vomiting, anhelation, and palpitations), chest Computed Tomography (CT), treatment methods, ventilator treatment parameters, and discharge outcome. In addition, laboratory tests, such as white blood cell (WBC) count, platelet (PLT) count, C-reactive protein (CRP), blood biochemical examination, electrolyte analysis, blood gas analysis, and lactate and coagulation routine examination were also collected. These variables were compared and analyzed for the different age and management groups. In addition, we obtained an APACHE II score and calculated the P/F value for patients with complete data.

Statistical Analysis

Distributions of variables were reported as the percentage, the mean ± standard deviation (normal distribution), and the interquartile range when the data was not normally distributed [M, (P25~P75)]. Chi-square or Fisher's exact tests were used to analyze categorical variables, whereas a Mann-Whitney U test was used to analyze continuous variables. Univariate analysis with the Cox proportional-hazards model was utilized to analyze the factors that influenced the outcome of patients with COVID-19. Receiver operating characteristic (ROC) analysis was used to establish the appropriate cutoff points for the APACHE II score and P/F value and to assess the sensitivity (Sn) and specificity (Sp) of the predictors for MV management. We also examined test parameters, including the area under the ROC curve (AUROC). A p-value less than 0.05 ($p < 0.05$) was considered statistically significant. Statistical analyses were performed with SPSS software (version 17.0, SPSS, Inc., Chicago, IL, USA).

Results

Demographics and Clinical Presentations

During the study period, 98 patients (56 males and 42 females, mean age: 66.73 ± 14.52 SD; range: 32-90 years) who were diagnosed with COVID-19 were enrolled in our study. Fever (64.3%), cough (37.8%), and chest distress (12.2%) were the major symptoms in patients with COVID-19. No statistically significant difference in clinical symptom distribution among different age groups was found (Table I). A history of hypertension was recorded in 42.7% of patients, and 17.3% had a history of coronary heart disease and diabetes

Table I. Demographics and clinical presentation of the patients with COVID-19.

Variables	Total (n = 98)		30-45 (n = 12)		46-60 (n = 24)		61-75 (n = 41)		> 75 (n = 21)		*p*-value
	N	%	N	%	N	%	N	%	N	%	
Gender											
Female	42	42.9	5	41.7	11	45.8	14	34.1	12	57.1	0.374
Male	56	57.1	7	58.3	13	54.2	27	65.9	9	42.9	
Fever											
Yes	63	64.3	6	50.0	15	62.5	27	65.9	15	71.4	0.657
Cough											
Yes	37	37.8	5	41.7	9	37.5	14	34.1	9	42.9	0.910
Weakness*											
Yes	7	7.1	0	0.0	3	12.5	2	4.9	2	9.5	0.574
Chest distress*											
Yes	12	12.2	1	8.3	3	12.5	6	14.6	2	9.5	0.970
Anhelation*											
Yes	8	8.2	0	0.0	2	8.3	4	9.8	2	9.5	0.869
Palpitation*											
Yes	3	3.1	1	8.3	1	4.2	0	0.0	1	4.8	0.210
Dyspnea*											
Yes	7	7.1	1	8.3	2	8.3	1	2.4	3	14.3	0.275
Diarrhea*											
Yes	6	6.1	1	8.3	0	0.0	3	7.3	2	9.5	0.460
History of hypertension											
Yes	41	42.7	2	18.2	9	40.9	17	41.5	13	59.1	0.160
History of CHD*											
Yes	17	17.3	1	8.3	4	16.7	4	9.8	8	38.1	0.048
History of DM*											
Yes	17	17.3	1	8.3	6	25.0	7	17.1	3	14.3	0.683

*Statistically significant according to the χ^2 test or Fisher's exact test when appropriate. CHD = coronary heart disease; DM=diabetes mellitus.

mellitus. The overall mortality rate was 26.53% (26/98), 30 patients (30.61%) were treated with MV, and the mortality rate was 73.33%.

Clinical Analysis of Patients with COVID-19

Patients were analyzed based on whether they underwent MV or not. Among all patients with COVID-19, 30 cases were treated with invasive MV (18 males and 12 females, mean age: 68.33 ± 12.36 SD; range: 37-90 years). There was no statistically significant difference in age distribution and gender in the group treated with mechanical ventilation (p = 0.109, p = 0.704, respectively) (Table II). Fever (70%), cough (30%), and dyspnea (16.7%) were the most common symptoms in patients who underwent MV. Dyspnea was more common in the MV group than in the non-MV group, with statistical significance (p = 0.045). Table III displays the differences in laboratory data between patients with and without MV treatment. The mean APACHE II score was 17.21 ± 6.74, and the mean P/F value was 107.47 ± 84.04 mmHg in the MV group. The peripheral blood WBC count, platelets, albumin, blood urea nitrogen, CK, CKMB, LDH, lactic acid, and blood calcium levels were significant factors that indicated the need for MV management (Table III). A Cox proportional-hazards regression analysis showed that the serum albumin level and APACHE II score were statistically different between the MV and the non-MV groups ($p < 0.05$) and were related to the increased risk of MV (Table IV).

Receiver Operating Characteristic Analysis of Predictors in Patients with COVID-19 Undergoing Mechanical Ventilation Treatment

The ROC curve in predicting the need for MV treatment indicated that the AUROC for the APACHE II score was 0.872 (Figure 1). The best cutoff value was 11.5 (sensitivity: 0.857; specificity: 0.811). The AUROC for the P/F ra-

Table II. Comparison of the clinical presentations of patients with COVID-19 based on management with MV or not.

Variables	No MV support (n = 68)		MV support (n = 30)		p-value
	N	69.39%	N	30.61%	
Gender					
Female	30	44.1	12	40	0.704
Male	38	55.9	18	60	
Age					
30-45	11	16.2	1	12.2	0.109
46-60	19	27.9	5	24.5	
61-75	26	38.2	15	41.8	
> 75	12	17.6	9	21.4	
Fever					
Yes	42	61.8	21	70	0.433
Cough					
Yes	28	41.2	9	30	0.293
Weakness					
Yes	6	8.8	1	3.3	0.584
Chest distress					
Yes	8	11.8	4	13.3	1.000
Anhelation					
Yes	4	5.9	4	13.3	0.400
Palpitation					
Yes	3	4.5	0	0.00	0.580
Dyspnea					
Yes	2	2.9	5	16.7	0.045
Diarrhea*					
Yes	5	7.6	1	3.3	0.733
History of hypertension					
Yes	30	44.1	11	36.7	0.491
History of CHD					
Yes	11	16.2	6	20.0	0.645
History of DM					
Yes	15	22.1	2	6.7	0.064

*Statistically significant according to the χ^2 test or Fisher's exact test when appropriate. MV= mechanical ventilation; CHD=coronary heart disease; DM=diabetes mellitus.

tio was 0.778 (Figure 2). The best cutoff value was 122.17 mmHg (sensitivity: 0.778; specificity: 0.774).

Discussion

The outbreak of the new coronavirus pneumonia has reached most countries and cities globally from the end of 2019 to the present, and it has had a major impact on human life and health. The clinical symptoms, the regularity of the disease, and its severity vary substantially among infected patients[3].

In our study, fever (64.3%), cough 37.8%), and chest tightness (12.2%) were the major symptoms in patients with COVID-19. Among mechanically ventilated patients, dyspnea seems to be more common, accounting for 16.7% of cases in this group ($p < 0.05$). Their APACHE II score was higher (17.21 ± 6.74), and the P/F ratio was lower (107.47 ± 84.04). It is easy to conclude that these patients met the criteria for acute respiratory distress syndrome (ARDS). However, it is frustrating that this subgroup of patients had such a high mortality rate, reaching 73.33% (22/30). This has been revealed by two previous researches on treatment in Wuhan, China, reporting that out of 33 patients with tracheal intubation, 32 (97%) died[4]. In another study[5], out of 37 patients, 30 were fatalities (81%). The clinical characteristics of 5,700 inpatients with COVID-19 in the New York area of the United States were recently reported and showed that 17.3% of the patients had a respiratory rate greater than 24 breaths/min during hospitalization. As of April 4, 2020, for patients requiring MV (n = 1151, 20.2%), 38 (3.3%) were discharged, 282 (24.5%) died, and 831 cases (72.2%) remained

Table III. Comparison of the laboratory tests of patients with COVID-19 based on management with MV or not.

Variables	No MV support			MV support			t/Z	*p*-value
	N	Mean	SD	N	Mean	SD		
WBC (×10^9/L)	66	5.73	3.08	30	7.84	5.09	2.514	0.014
CRP (mg/L)	60	54.59	43.22	27	71.75	33.01	1.835	0.07
PLT (×10^9/L)	66	176.13	87.79	30	132.20	72.25	-2.395	0.019
ALB (g/L)	68	35.91	5.05	30	31.47	5.02	-4.020	0.000
GLO (g/L)	68	27.41	4.82	30	27.72	6.72	0.229	0.820
ALT (U/L)	67	21 (30~52)		30	21 (25.50~53.25)		-0.523	0.601
AST (U/L)	67	23 (30~51)		30	28.5 (43~58.25)		-1.585	0.113
DB (mmol/L)	68	5.4 (7.55~9.38)		30	5.1 (9.85~14.33)		-1.989	0.047
BUN (mmol/L)	67	4.35 (3.23~5.96)		30	6.26 (4.94~8.84)		-3.653	0.000*
Creatinine (mmol/L)	67	62.81 (45.82~78.23)		30	64.50 (52.23~86.57)		-1.210	0.226
PT	67	12.09	1.56	27	12.40 (11.50~13.90)		-1.673	0.094
APTT	67	39.86	7.78	27	36.27	9.74	-1.878	0.063
Potassium (mmol/L)	65	4.05	0.64	30	3.98	0.62	-0.509	0.612
Sodium (mmol/L)	65	137.74	4.75	30	139.25	7.02	1.231	0.221
Calcium (mmol/L)	65	2.13 (1.99~2.23)		30	2.06 (1.16~2.16)		-2.015	0.044*
Lactate (mmol/L)	29	1.63	0.83	23	2.54	1.86	2.179	0.038
LDH (U/L)	52	323 (238.75~428.75)		25	599 (398~811.5)		-4.237	0.000*
CK (U/L)	51	94 (36~166)		25	196 (57.5~481.5)		-2.173	0.030*
CKMB (U/L)	53	2.30,0.50,104.00		26	7.55 (1.95~19.7)		-2.354	0.019*
NT-proBNP (pg/mL)	26	122.45 (32.88~301.25)		24	209.15 (88.08~445.18)		-1.078	0.281*
APACHEII	37	9.49	3.66	28	17.21	6.74	5.626	0.000
P/F	31	223.75	133.82	27	107.47	84.04	-4.014	0.000

*Statistically significant according to the Mann-Whitney U test. IQR = interquartile range, M(P25~P75); MV = Mechanical ventilation; WBC = white blood count; CRP=C-reactive protein; CK = creatine phosphokinase; CKMB = creatine phosphokinase-MB; AST = aspartate aminotransferase; ALT=alanine aminotransferase; BUN=blood urea nitrogen; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; APACHE II=Acute Physiology and Chronic Health Evaluation II; P/F=PaO_2/FiO_2.

hospitalized[6]. These data indicate that this group of patients, who require MV *via* endotracheal intubation, may have a poor prognosis.

Mechanical ventilation is an important aspect of the management of critically ill patients. In the case of moderate to severe ARDS or failure of other organs, noninvasive ventilation support has a higher risk of failure. In these cases, the risk of delayed MV should be carefully evaluated[7]. Therefore, identifying and assessing factors that predict the need for patients to undergo invasive ventilation is critical. However, the factors associated with the early prediction of the need for MV support in patients with COVID-19 are still unclear. Our results revealed several factors that may predict the need for MV support in patients with COVID-19. These include dyspnea, APACHE II score, and P/F ratio. Moreover, increased WBC count, decreased platelets, low albumin levels, increased urea nitrogen, increased levels of myocardial enzymes CK, CKMB, and LDH, high lactate, and low blood calcium tests were important factors that helped us detect the need for MV support early in these patients. Finally, we performed a Cox proportional-hazards regression analysis and found that low albumin levels and APACHE II scores were important factors that predicted the need for mechanical ventilation.

Table IV. Analysis of factors influencing MV that was performed in patients with COVID-19.

Variables	β	S.E.	Wald	Exp (β)	95% CI for Exp (β)	*p*-value
ALB	-0.140	0.065	4.724	0.869	0.766-0.986	0.030*
APACHE II	0.166	0.075	4.937	1.181	1.020-1.367	0.026*

*Statistically significant according to a Cox proportional-hazards regression analysis. IQR = interquartile range; MV = Mechanical ventilation; Exp (β): Hazard Ratio; 95% CI for Exp(β): Univariate Analysis 95% CI.

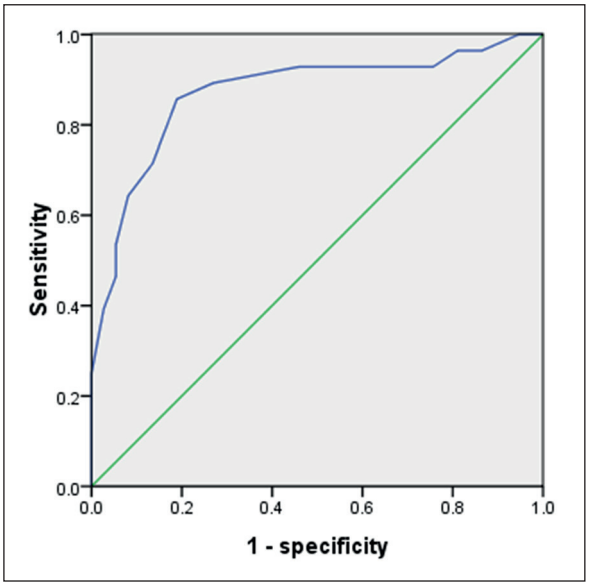

Figure 1. Receiver operating characteristic curve for APACHE II score in predicting the need for mechanical ventilation treatment. The area under the curve was 0.872. The best cutoff value for APACHE II score was 11.5 (sensitivity: 0.857; specificity: 0.811).

The APACHE II score system has been widely used in intensive care units, respiratory intensive care units, and surgical intensive care units to determine the severity of disease and predict the clinical process and patient outcomes[8-10]. A prognostic risk factor study[11] of patients with acute myocardial infarction showed that patients requiring MV had a higher APACHE II score, and the score was an independent risk factor for death. Our study showed significant differences in the APACHE II score between the patients with COVID-19 with and without MV support. Moreover, our results suggest that the most appropriate cutoff value of the initial APACHE II score in predicting MV support was 11.5.

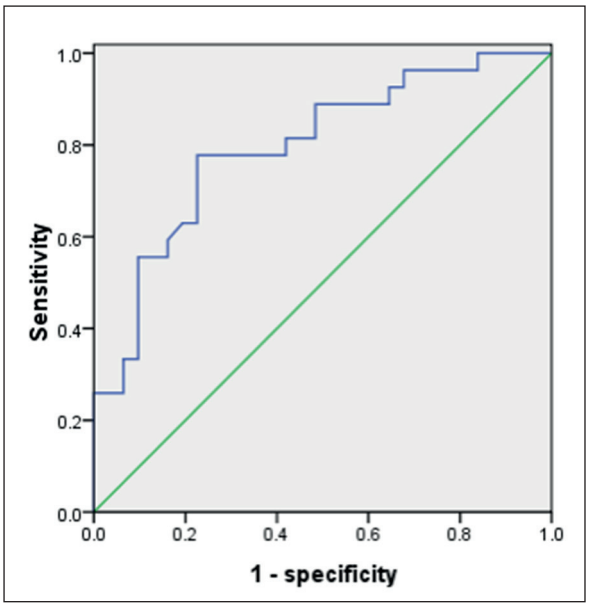

Figure 2. Receiver operating characteristic curve for the PaO_2/FiO_2 ratio in predicting the need for mechanical ventilation treatment. The area under the curve was 0.778. The best cutoff value for the PaO_2/FiO_2 ratio was 122.17 mmHg (sensitivity: 0.778; specificity: 0.774).

According to the Berlin standard of ARDS[12] and the consensus of current Chinese experts[13], invasive MV is recommended as the first choice for patients with moderate or severe ARDS (P/F $\leq$ 150 mmHg). In addition, we found significant differences in P/F ratios between the patients with COVID-19 with and without MV support, with the most appropriate cutoff value of the initial P/F ratio in predicting Mechanical ventilation (MV) support being 122.17 mmHg. Our results suggest that physicians should be aware of these clinical factors in patients with COVID-19 to detect the need for MV support earlier and more accurately. In other words, if patients present with these risk factors, they are likely to need early and aggressive therapeutic intervention.

This study has some limitations. First, since it is a retrospective study, with the participation of three designated hospitals, some details of the patients' clinical data, physical examination, and laboratory examination may not have been rigorously documented. Second, since there is no uniform standard or guideline on how to give patients respiratory support or when to give them MV treatment, there may have been differences in the experience and standards of individual clinicians in the three designated treatment units. Finally, some patients who would have been required to receive MV support or to be admitted to ICU did not receive these interventions due to various reasons, such as family members' refusal. These limitations may have led to some bias in the available data regarding the factors associated with COVID-19 and the need for MV management.

Conclusions

Summarily, the overall mortality rate of COVID-19 is relatively low, but the prognosis of patients receiving MV treatment is frustrating. Dyspnea, increased WBC count, decreased pla-

telets, low albumin levels, increased urea nitrogen, increased levels of myocardial enzymes CK, CKMB, and LDH, high lactate, and low blood calcium test results may indicate that the patient is at an increased risk for MV support. Most importantly, a cutoff value for the initial APACHE II score of >11.5 and the initial P/F ratio of <122.17 mmHg should be considered a warning sign in patients with COVID-19 and guide the clinician in evaluating the need for MV support.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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