

Invasive Mechanical Ventilation May Be an Important Factor of Mortality in Severe/Critical COVID-19 Pneumonia: A Retrospective Cohort Study

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Research

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Abstract

Background: Many of severe COVID-19 patients are admitted to the hospital or even to the Intensive Care Unit(ICU). The present study was aimed to investigated the risk factors in death from COVID-19.

Methods: In this retrospective study, all inpatients confirmed severe or critical COVID-19 from two tertiary hospital in Huangshi were included, who had been discharged or died by March19,2020. Demographic,clinical,treatment,laboratory data and information were extracted from electronic medical records and compared between survivors group and non-survivors group. The univariable and multivariable logistic regression analysis was used to analyze the risk factors associated with in-hospital death.

Results: 81 patients were included in this study, of whom 55 were discharged and 26 died in hospital. In all patients, 36(44.4%) patients had comorbidity, including hypertension(27[33.3%]), diabetes(11[13.6%]) and coronary heart disease (CHD)(11[13.6%]), and 16(19.8%) patients accompanied with more than 2 kinds of underlying diseases. The proportion of CHD in non-survivors group was significantly higher than that in survivors group(26.9% vs 7.3%, $P=0.032$), but there were no differences in hypertension, diabetes and COPD between the non-survivors group and the survivors group. Multivariable logistic regression analysis showed increasing odds of in-hospital death associated with aspartate aminotransferase(AST) and invasive mechanical ventilation (IMV) ($P<0.001$)($P=0.017$).

Conclusions: Invasive Mechanical Ventilation may contribute to mortality of severe/critical COVID-19 pneumonia, and with higher AST at admission was one of the indicators of poor prognosis.

Trial registration: Chinese Clinical Trial Registration; ChiCTR2000031494; Registered 02 April 2020; <http://www.medresman.org>

Backgrounds

SARS-CoV-2, a positive-sense single-stranded RNA virus and is taxonomically a member of the beta coronavirus genus, has caused a pandemic of COVID-19 worldwide with a mortality rate of about 2.7% to date (October 27, 2020)[1]. Study had illustrated the mortality is related with age, underlying disease such as hypertension, diabetics, and autoimmune hypimmunity, and so on[2]. It has been reported the COVID-19 is generally susceptible to the population, and may progresses rapidly into severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome(MODS), and even death[3]. It has confirmed the virus transmitted human-to-human mainly via respiratory droplets and intimate contact[4]. Previous studies have described the general clinical characteristics and epidemiological findings of patients with COVID-19. Some countries are currently experiencing a second wave of outbreaks, and more patients will have to suffer the threat of death. This article is aimed to study the indicators related to the prognosis of the severe/critical patients.

Methods

This is a retrospective study of 81 patients who confirmed with COVID-19 at Huangshi Center Hospital, China before March 19, 2020. As the study does not involve patients' privacy, the informed consent can be exempted. Electronical medical records include demographics, clinical manifestation, comorbidities, and laboratory data of 81 hospitalized COVID-19 patients.

According to the diagnosis and treatment of Novel Coronavirus Pneumonia (trial version 5) of China, patients with the following clinical signs were considered to have severe pneumonia: respiratory frequency $\geq 30/\text{min}$, oxygen saturation $\leq 93\%$ at rest and oxygenation index $\leq 300 \text{ mmHg}$; Pulmonary imaging showed significant progression of $> 50\%$ within 24–48 hours were also included.

The following situation is considered critical pneumonia: respiratory failure and the need for mechanical ventilation; shock; combined with other organ failure requires intensive care.

All cases were divided into non-survivor and survivor groups for comparison. Demographic, symptoms, laboratory data and clinical management were extracted from electronic medical records. Datas on lymphocyte (LYM) count, alanine transaminase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), urea, C-reactive protein (CRP), D-dimer and procalcitonin (PCT) levels were included. These datas were acquired by physicians and were the results of an examination at the very beginning after admission.

Statistics:

The continuous variables were either presented as means and compared using t-tests if they were normally distributed or were described using medians. The Mann–Whitney U test was used for comparisons. Categorical variables were presented as count (%) and compared by the Chi-squared test or Fisher's exact test. The area under the curve (AUC) and the 95% confidence interval (CI) of the receiver operator characteristic (ROC) curve and multivariable logistic regression analysis was computed using the predicted probability of the severe COVID-19. Use R software for statistics and a P-value < 0.05 was considered to be statistically significant.

Results

Clinical characteristics and symptoms on admission

A total of 81 patients were enrolled in this retrospective study, of whom 26 died and 55 were discharged. The demography and epidemiology of all confirmed COVID-19 patients are shown in Table 1. The median age of all patients was 64 years old. There was a statistically significant difference in age between survivors group and non-survivors group (60 vs 68.5, $p = 0.0016$), with males accounting for 56.8% cases. 44.4% cases had one underlying disease including hypertension, diabetes mellitus, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), malignancy, and cerebral infarction. Among these, hypertension being the most common comorbidities (27[33.3%]), followed by diabetes

(11[13.6%]), coronary heart disease (11[13.6%]) and malignancy (4[4.9%]). Rate of patients with CHD in non-survivors group was significantly higher than that in the survivors group (26.9% vs 7.3%, $P = 0.032$). Compared with survivors group, the non-survivors group had a higher levels of PCT(0.1 vs 0.3, $P = 0.025$). Incidence of ARDS(23.1% vs 5.5%, $P = 0.027$), MODS(26.9% vs 0.0%, $P < 0.001$), and renal dysfunction in non-survivors group was also significantly higher than that in survivors group.

Table 1
Demographic, clinical, laboratory findings and treatments of patients on admission

Characteristics	Total N = 81	Survivors N = 55	Non-survivors N = 26	P- value
Demographics				
Age(yrs)	64.0 (50.0,71.0)	60.0 (49.0,69.0)	68.5 (62.0,83.0)	0.0016
Gender				1.000
male	46 (56.8%)	31 (56.4%)	15 (57.7%)	
female	35 (43.2%)	24 (43.6%)	11 (42.3%)	
Days from onset to admission	7.0 (4.0,10.0)	7.0 (4.5,10.0)	6.0 (4.0,8.0)	0.664
In-hospital days	20 (16.0,27.0)	23 (17.5,29.5)	15 (10.0,18.0)	< 0.001
Comorbidities				
Hypertension	27 (33.3%)	17 (31.0%)	10 (38.5%)	0.647
Diabetes	11 (13.6%)	9 (16.4%)	2 (7.7%)	0.489
CHD	11 (13.6%)	4 (7.3%)	7 (26.9%)	0.032
Malignancy	4 (4.9%)	1 (1.8%)	1 (3.8%)	0.095
COPD	2 (2.5%)	0 (0%)	2 (7.7%)	0.100
Cerebral infarction	5 (6.2%)	3 (5.5%)	2 (7.7%)	0.654
Symptoms and complications				
Fever	68 (84.0%)	48 (87.3%)	20 (76.9%)	0.527
Cough	38 (46.9%)	25 (45.5%)	13 (50%)	0.885
Tussiculation	2 (2.5%)	2 (3.6%)	0 (0%)	0.828
Dyspnea	14 (17.3%)	9 (16.4%)	5 (19.2%)	0.7602
Hypertension	2 (2.5%)	1 (1.8%)	1 (3.8%)	1

*Data are median (IQR), n (%), or n/N (%). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.

Abbreviation: CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome; Cr: creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reaction protein; LYM: lymphocyte; NIV: non invasive ventilator; IMV: invasive mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation

Characteristics	Total N = 81	Survivors N = 55	Non-survivors N = 26	P-value
Fatigue/myalgia	4 (4.9%)	4 (7.3%)	0 (0%)	0.2999
Abdominal pain or Diarrhea or Vomiting	5 (6.2%)	4 (7.3%)	1 (3.8%)	1
Headache	3 (3.7%)	2 (3.6%)	1 (3.8%)	1
Pulse	89.0 (80.0,91.0)	89.0 (80.0,90.0)	89.0 (85.0,95.0)	0.187
Respiratory rate	24.0 (20.0,28.0)	22.0 (20.0,28.0)	25.5 (21.0,29.0)	0.248
ARDS	9 (11.1%)	3 (5.5%)	6 (23.1%)	0.027
MODS	7 (8.6%)	0 (0%)	7 (26.9%)	< 0.001
Laboratory findings				
LYM count	0.7 (0.5,1.0)	0.73 (0.5,1.0)	0.6 (0.5,0.8)	0.174
AST	38.0 (29.0,50.8)	32.0 (26.0,43.0)	48 (38.0,61.0)	< 0.001
ALT	28.0 (20.0,38.0)	27.0 (19.0,38.5)	31.5 (21.0,38.0)	0.354
Urea	4.5 (3.2,6.2)	4.1 (3.1,5.4)	5.5 (4.5,7.9)	0.020
Cr	64.2 (49.0,78.7)	62.0 (46.8,73.4)	74.0 (53.5,89.7)	0.006
CRP	59.4 (33.9,72.9)	56.7 (325,72.1)	66.1 (46.4,91.1)	0.167
D-Dimer	0.4 (0.1,0.8)	0.3 (0.1,0.8)	0.6 (0.2,1.4)	0.097
PCT	0.2 (0.1,0.5)	0.1 (0.1,0.4)	0.3 (0.1,0.7)	0.025
Treatment				
Antibiotic	80 (98.8%)	54 (98.2%)	26 (100%)	1
Antiviral	81 (100%)	55 (100%)	26 (100%)	1
*Data are median (IQR), n (%), or n/N (%). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.				
Abbreviation: CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome; Cr: creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reaction protein; LYM: lymphocyte; NIV: non invasive ventilator; IMV: invasive mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation				

Characteristics	Total N = 81	Survivors N = 55	Non-survivors N = 26	P-value
Glucocorticoids	72 (88.9%)	46 (83.6%)	26 (100%)	0.052
Immune globulin	70 (86.4%)	46 (83.6%)	24 (92.3%)	0.489
Recovered plasma	8 (9.9%)	4 (7.3%)	4 (15.4%)	0.262
Heparin	31 (33.2%)	20 (36.4%)	11 (42.3%)	0.788
Oxygen	77 (95.1%)	52 (94.5%)	25 (96.2%)	1
NIV	40 (49.4%)	17 (30.9%)	23 (88.5%)	< 0.001
IMV	22 (27.2%)	4 (7.3%)	18 (69.2%)	< 0.001
CRRT	3 (3.7%)	0 (0%)	3 (11.5%)	0.030
ECMO	0	0	0	1
*Data are median (IQR), n (%), or n/N (%). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.				
Abbreviation: CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome; Cr: creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reaction protein; LYM: lymphocyte; NIV: non invasive ventilator; IMV: invasive mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation				

Treatments

All patients received antiviral treatment (81 [100%]). Most patients received antibiotics (80 [98.8%]), glucocorticoids (72 [88.9%]), immune globulin (70 [86.4%]), and 8 [9.9%] patients received recovered plasma. 77 patients received oxygen therapy. 40(49.4%) and 22(27.2%) of total patients received NIV and IMV, respectively. Continuous renal replacement therapy(CRRT)was given to 3(11.5%) patients. There are significantly higher rate of application of NIV(88.5% vs 30.9%, $P < 0.001$), IMV(69.2% vs 7.3%, $P < 0.001$) and CRRT (11.5% vs 0.0%, $P = 0.03$) in non-survivors group than that in survivors group. No patients received extracorporeal membrane oxygenation (ECMO) as rescue therapy in this study. The average length of hospital stay in the non-survivors group was significantly shorter than that in the survivors group ($P < 0.001$)(Table 1).

Results Of Univariable And Multivariable Logistic Regression Analysis

In univariable analysis, the elements mentioned above including age, in-hospital days, patients with CHD, ARDS, the count of AST, NIV and IMV were associated with death. We included 81 patients with complete data for the above 7 variables with statistical significance (26 non-survivors and 55 survivors) in the multivariable logistic regression model. The results indicated that, the independent risk factors for death were AST (95% CI: 1.01–1.06; $p = 0.017$) and IMV (95% CI: 8.2-1113.74; $p \leq 0.001$) (Table 2, 3 and Fig. 1).

Table 2
Statistics of IMV in 81 patients

	Non-survivors	Survivors	χ^2 test
IMV	18	4	P < 0.001
Non-IMV	8	51	
Total	26	55	
Abbreviation: IMV: invasive mechanical ventilation			

Table 3
Risk factors associated with in-hospital death

Characteristics	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value
Demographics and clinical characteristics				
Age	1.06 (1.03,1.11)	0.002	1.07 (1.00,1.15)	0.052
Female sex (vs male)	0.95 (0.36,2.43)	0.910		
Days from onset to admission	1.03 (0.96,1.13)	0.397		
In-hospital days	0.80 (0.70,0.88)	0.0001		
Comorbidity present (vs not present)				
Hypertension	1.40 (0.52,3.70)	0.502		
Diabetes	0.43 (0.06,1.82)	0.299		
CHD	4.70 (1.27,19.69)	0.023	1.83 (0.24,14.60)	0.556
Symptoms and complications				
Fever	0.486 (0.14,1.68)	0.242		
Cough	1.20 (0.47,3.08)	0.702		
Dyspnea	1.22 (0.34,3.98)	0.750		
Hemoptysis	2.16 (0.08,56.12)	0.591		
Pulse	1.03 (0.99,1.08)	0.089		
Respiratory rate	1.05 (0.96,1.15)	0.284		
ARDS	5.20 (1.25,26.56)	0.029	0.27 (0.021,3.02)	0.291
Laboratory findings				
LYM Count	0.59 (0.23,2.05)	0.441		
AST	1.02 (1.01,1.04)	0.011	1.03 (1.01,1.06)	0.017
ALT	1.00 (0.98,1.02)	0.901		
Urea	0.99 (0.32,0.89)	0.383		
Cr	1.02 (0.99,1.04)	0.079		

Abbreviation: CHD: coronary heart disease; ARDS: acute respiratory distress syndrome; LYM: lymphocyte; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine; CRP: C-reaction protein; NIV: non invasive ventilator; IMV: invasive mechanical ventilation

Characteristics	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value
CRP	1.00 (0.99,1.02)	0.170		
D-Dimer	1.47 (1.00,2.25)	0.054	1.24 (0.64,2.40)	0.514
Treatment				
Immune globulin	2.34 (0.55,16.21)	0.299		
Recovered plasma	2.318 (0.51,10.63)	0.263		
NIV	17.14 (5.12,79.47)	< 0.001	1.30 (0.16,9.57)	0.796
IMV	28.69 (8.42,121.62)	< 0.001	68.10 (8.20,1113.74)	< 0.001
Abbreviation: CHD: coronary heart disease; ARDS: acute respiratory distress syndrome; LYM: lymphocyte; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine; CRP: C-reaction protein; NIV: non invasive ventilator; IMV: invasive mechanical ventilation				

Discussion

To date, approximately 43,147,000 confirmed cases, and 1,155,553 deaths of COVID-19 have been reported (October 27, 2020). Elderly COVID-19 patients have been documented which would be faced with a higher risk of death[5]. It also been reported hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease are major risk factors for patients with COVID-19[2]. Similar to previous studies[6, 7], the median age of non-survivors group was significant older than that of survivors group and the most common comorbidities of the COVID-19 patients in our cohort are hypertension and diabetes. Higher levels of PCT maybe indicated more serious pathogen infections in non-survivors group. The increased incidence of ARDS and MODS may be associated with older age and more underlying diseases in non-survivors group.

Our data showed that the levels of AST has the varying degree elevation in both two groups, suggesting that acute liver damage was frequent in COVID-19 patients. This phenomenon was also observed in other reports[3, 8]. The possible causes of liver damage are immune mediated damage as a result of the severe inflammatory response following COVID-19 infection, direct cytotoxicity as a result of active viral replication, anoxia, and drug-induced liver injury[9, 10]. Observational studies have found that liver injuries was generally mild or temporary in COVID-19 patients though the severe liver damage could be seen, and it was clear that significant liver injury occurs almost only in those with severe symptoms[3, 8]. Our result showed that higher levels of AST at admission had a higher mortality rate. It means that the patients with abnormal liver function was more likely to develop severe pneumonia or even to death. The majority of studies have revealed that D-dimer might be a manifestation of severe virus infection. Zhou F et al found that D-dimer greater than 1 µg/ml was a risk factor of poor prognosis for COVID-19[11], and Tang N et al

also reported high levels of D-dimer were associated with 28-day mortality in COVID-19[12]. Therefore, similar to D-dimer, we believe that AST also can be an important indicator to predict the prognosis of the COVID-19 patients.

As we known, both ALT and AST are one of the indicators of liver function. In present study, whereas, we only found the association between AST and prognosis of COVID-19 patients, but not found in ALT. It might be due to the fact that ALT and AST are distributed in different locations in hepatocytes. Specifically, ALT is mainly distributed in the cytoplasm of liver cells, which reflects damage to liver cell membranes if the levels of ALT are elevated, and AST is mainly distributed in the mitochondria and cytoplasm of liver cells, which reflects damage to organelle if the levels of AST are elevated[13]. In addition, the levels of AST in cardiomyocytes were higher than that in liver cells, and recent studies have also shown that SARS-CoV-2 could attack multiple organs, including the heart[14]. According to the above, we speculate that SARS-CoV-2 may cause damage to tissue cells by blocking mitochondrial function. Nevertheless, the exact molecular mechanism by how the virus causes damage to cell function is not clear, and still needs further research to be illustrated.

It was well known that IMV is an important way to improve oxygenation in patients with ARDS or severe pneumonia. Whereas, the application of IMV in severe COVID-19 patients is controversial. One meta-analysis which included 37359 patients revealed that the using of IMV for COVID-19 with severe ARDS increased mortality from disease[15]. Another study showed that the timing of IMV application is crucial to the prognosis of the severe COVID-19 patients. They used a novel indicator, cumulative oxygen deficit (COD), which represents the magnitude and duration of hypoxemia. The authors suggest IMV should be the preferred ventilatory support once the COD reaches 30[16].

In our multivariable logistic regression analysis, we found that IMV was an independent risk factor for severe COVID-19 patients. Studies have reported that IMV may not improve the mortality in COVID-19 patients, and IMV can also cause many complications which including barotrauma, ventilator-related infection, volume imbalance, and so on[17, 18]. Pathological findings had indicated that there had the formation of mucus plugs and the secretions in the airway were viscous in COVID-19 patients[19]. Therefore, we speculated that early application of IMV may promote the delivery of mucus to the distal end of the airway, which may lead to deteriorating oxygenation in patients. In our clinical experience, at the early stages of hypoxia, high-flow oxygen therapy via nasal cannula (HFNC) may be a better option to improve patient oxygenation. Absolutely, when patients suffer from severe hypoxemia, shock, disturbance of consciousness, or even respiratory and cardiac arrest, IMV should be applied timely. Further research is still needed regarding the timing of IMV applications.

Conclusion

In conclusion, AST and IMV were independent risk factors for the severity of COVID-19. Additional attention should be paid with elevated AST on admission and IMV in the course of COVID-19.

Limitations

The present study had some limitations. First, 81 patients were included in the present study, and it is necessary to expand sample size cohort to verify our conclusions. Second, our study is a retrospective study, so the observational indicators were not strictly followed the criteria of prospective cohort studies. We look forward to prospective studies with larger samples to increase our understanding of the application of IMV for COVID-19.

Abbreviations

COVID-19: coronavirus disease 2019; CRP:C-reaction protein; ARDS:acute respiratory distress syndrome; MODS:multiple organ dysfunction syndrome; CHD:coronary heart disease; COPD:chronic obstructive pulmonary disease; LYM:lymphocyte; ALT:alanine aminotransferase; AST:aspartate aminotransferase; Cr:creatinine; NIV:non invasive ventilator; IMV:invasive mechanical ventilation; CRRT:continuous renal replacement therapy; ECMO:extracorporeal membrane oxygenation; AUC:the area under the curve; ROC:receiver operator characteristic.

Declarations

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Authors' contributions

J.W., L.SHI., Z.C., R.L., X.J, W.Z. and T.H.conceived and designed the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.W., L.SHI., Y.Z., and N.J. contributed to the analysis of the infection status and the writing of the paper. X.C, M.W., K.D., L.Shu., X.W., Y.C., W.H. and J. Y. assisted in data collection, extraction and evaluation of the eligibility of the original data. J.W. L.SHI., Z.P and C.N. analyzed the data. J.W, L.SHI., Z.C., and G.F. interpreted the data and contributed to the writing of the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The majority of the data generated or analyzed during this study are included in this article. Unpublished data are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

It was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Huangshi Hospital of Traditional Chinese Medicine (No. HSZYPJ-2020-009-01).

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Figures

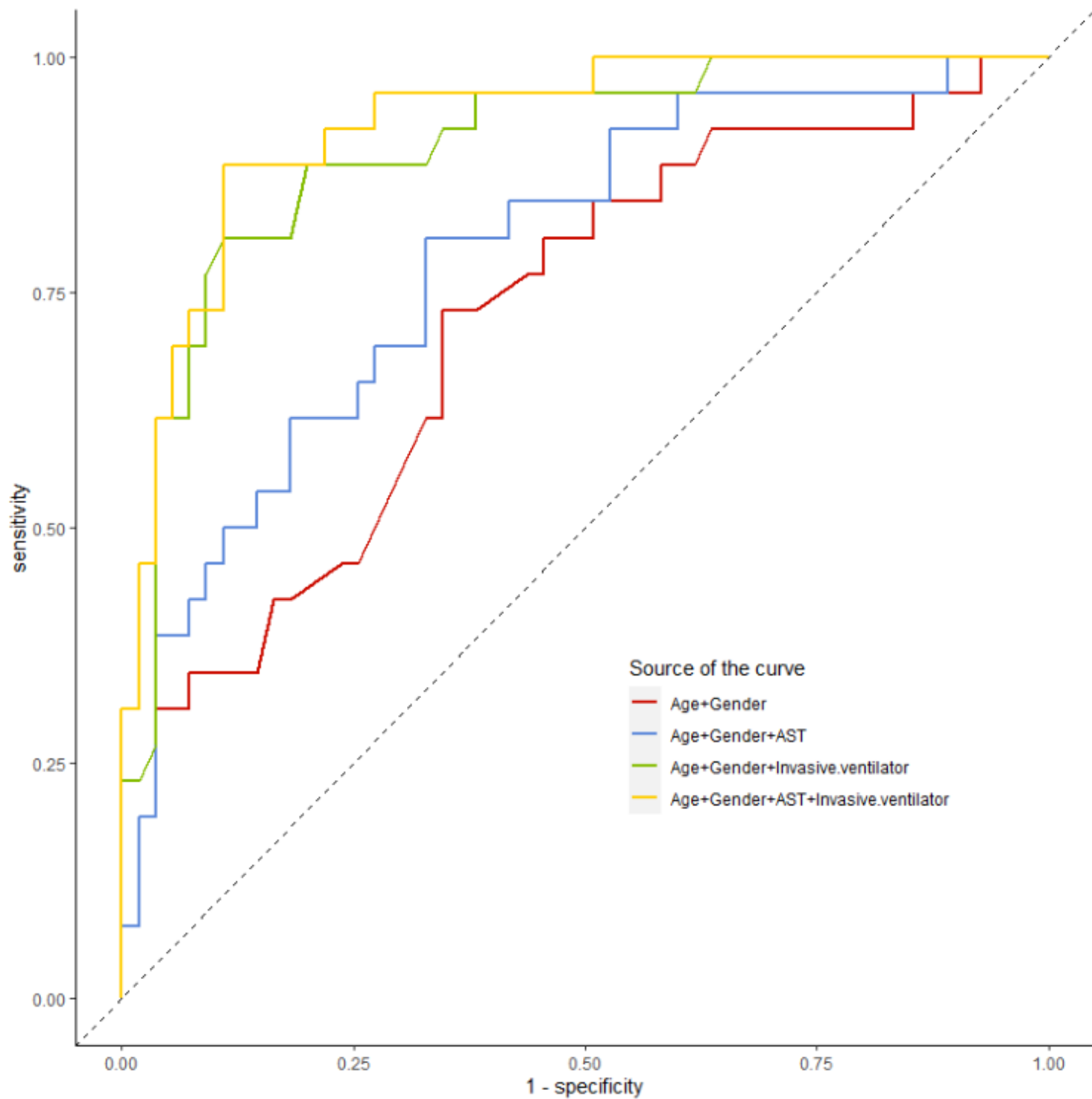


Figure 1

Receiver operator characteristic curves comparing the potential of different variables to predict the severe/critical COVID-19.