

Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized

Patients in Wuhan, China

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Summary: This study identified 27 risk factors associated with COVID-19 clinical outcomes. The administration of hypnotics was significantly associated with favorable outcomes for COVID-19. Novel risk factors, such as higher hypersensitive troponin I, were found to predict poor clinical outcomes.

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Abstract

Background

With evidence of sustained transmission in more than 190 countries, coronavirus disease 2019 (COVID-19) has been declared a global pandemic. Data are urgently needed about risk factors associated with clinical outcomes.

Methods

A retrospective review of 323 hospitalized patients with COVID-19 in Wuhan was conducted. Patients were classified into three disease severity groups (non-severe, severe, and critical), based on initial clinical presentation. Clinical outcomes were designated as favorable and unfavorable, based on disease progression and response to treatments. Logistic regression models were performed to identify risk factors associated with clinical outcomes, and log-rank test was conducted for the association with clinical progression.

Results

Current standard treatments did not show significant improvement in patient outcomes. By univariate logistic regression analysis, 27 risk factors were significantly associated with clinical outcomes. Multivariate regression indicated age over 65 years ($p<0.001$), smoking ($p=0.001$), critical disease status ($p=0.002$), diabetes ($p=0.025$), high hypersensitive troponin I (>0.04 pg/mL, $p=0.02$), leukocytosis ($>10 \times 10^9/L$, $p<0.001$) and neutrophilia ($>75 \times 10^9/L$, $p<0.001$) predicted unfavorable clinical outcomes. By contrast, the administration of hypnotics was significantly associated with favorable outcomes ($p<0.001$), which was confirmed by survival analysis.

Conclusions

Hypnotics may be an effective ancillary treatment for COVID-19. We also found novel risk factors, such as higher hypersensitive troponin I, predicted poor clinical outcomes. Overall, our study provides useful data to guide early clinical decision making to reduce mortality and improve clinical outcomes of COVID-19.

Key words: COVID-19, Risk Factor, Clinical Outcome, Hypnotics, Obesity

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially lethal respiratory illness caused by a newly identified coronavirus, named SARS coronavirus 2 (SARS-CoV-2), which was first recognized in December 2019 in Wuhan, in Hubei Province, China.^{1,2} COVID-19 has spread rapidly to more than 190 countries, and as of April 7, 2020, 1,431,689 confirmed cases and 82,074 deaths have been officially reported worldwide.³⁻⁷ With sustained transmission on six continents, the World Health Organization (WHO) has recently declared COVID-19 as a global pandemic.

Most previous studies of COVID-19 have focused primarily on epidemiological and clinical characteristics.⁸⁻¹³ Wang and co-workers compared the clinical features of 138 hospitalized patients with non-severe and severe COVID-19.¹⁰ Guan and colleagues updated the clinical characteristic and disease severity in 1,099 laboratory-confirmed cases throughout China.¹² Only a few studies have investigated risk factors associated with clinical outcomes.^{14,15} So, it is urgent to identify potential novel risk factors and treatments associated with patient-centered outcomes of COVID-19.

In this study, we analyzed the initial clinical presentation and baseline laboratory test results, as well as clinical course, of 323 hospitalized patients with COVID-19, in Wuhan, to identify risk factors associated with clinical outcomes for improving management guidelines.

METHODS

Study design and participants

The institutional ethics board of Tianyou Hospital, an affiliate of the Wuhan University of Science and Technology, approved the conduct of this retrospective review. Oral consent was obtained from patients and written informed consent was waived. Tianyou Hospital is one of several designated hospitals for the treatment of COVID-19 in Wuhan.

Of 330 patients with COVID-19 hospitalized from January 8 to February 20, 2020, seven patients were excluded due to incomplete medical records because they elected to be transferred to other hospitals, leaving 323 patients in the study. The final follow-up date was March 10, 2020.

Data collection

Clinical signs, disease onset, laboratory tests (including RT-PCR and chest computer tomography, or CT), treatments, co-morbidities, complications, and outcomes data were collected from electronic medical records (EMR). All raw data were initially evaluated by trained physicians. More details about laboratory procedures are provided in the appendix.

Case definition and classification

Diagnosis complied with the WHO interim guidance¹⁶ and the guidelines of COVID-19 diagnosis and treatment trial (5th edition), by the National Health Commission of the People's Republic of China.¹⁷

COVID-19 diagnosis was based on (1) the exclusion of other known infectious and non-infectious causes of pneumonia; (2) exposure history in Wuhan in the most recent 14 days or contact history with a confirmed COVID-19 patient or COVID-19 cluster; and (3) clinical presentation of fever and respiratory symptoms, characteristic CT image, and/or leukopenia and lymphopenia. All COVID-19 patients had to have an exposure history and at least two of the three clinical presentation criteria.

Based on the clinical presentation at the time of admission, patients were categorized into one of three groups: non-severe, severe and critical. And their initial clinical presentation and test results at baseline were associated with either favorable or unfavorable clinical outcomes. More details about clinical classification are provided in the appendix.

Clinical outcomes

Disease improvement or favorable clinical outcome included full recovery and discharge, progression from critical/severe to non-severe disease status, PCR positive to negative and/or maintenance of non-severe status. Disease progression or unfavorable clinical outcome included death, progression from non-severe to severe/critical disease status or severe to critical status, and/or maintenance of severe or critical status.

Statistics analysis

Chi-square test or Fisher exact test was used for categorical variables measurements. For continuous variables, student T-test or Mann-Whitney test was used. Multiple imputation was conducted to handle missing data.¹⁸ Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression models. For survival analysis, the survival time was defined as the interval from the date of admission to the date of death or discharge. The association of risk factors with clinical outcome was analyzed using the Kaplan-Meier method and log-rank test. All analyses were implemented with R software (version 3.6.2) or Statistical Analysis System (SAS) software (version 9.4, SAS Institute Inc., Cary, NC). All *P* values were two-sided, and those < 0.05 were considered as statistically significant.

RESULTS

Clinical characteristics

Of the 323 COVID-19 patients, 186 (57.6%) were RT-PCR positive and 137 (42.4%) patients were RT-PCR negative but had typical chest CT image, respiratory symptoms and compatible blood test results at the time of admission. At the end of the study, 252 patients had recovered and were discharged, 35 patients had died (overall case fatality rate, 10.8%), and 36 patients were still hospitalized.

Based on their initial clinical presentation, the 323 patients were classified into the non-severe (151), severe (146) and critical (26) disease groups (Table 1). There was no gender difference between the three groups. The median age of patients was 61 years (range, 23–91). Patients over 65 years were overrepresented within the severe (43.2%, 63/146) and critical (57.7%, 15/26) disease groups.

On admission, fever (83.9%, 271/323) and cough (50.8%, 164/323) were the most common symptoms, while dyspnea (4.3%, 14/323), chest distress (0.9%, 3/323) and headache (0.9%, 3/323) were uncommon.

Clinical outcomes

Test results at baseline rather than the highest value during hospitalization were used to predict clinical outcome. Patients were enrolled from January 8 to February 20, 2020, and the final follow-up date was March 10, 2020. The median hospital length of stay was 18 (11–21) days. Favorable outcomes were recorded in 260 patients and unfavorable outcomes in 63 patients. Among the three disease severity groups, 86.8% (131/151) and 84.9% (124/146) of patients in the non-severe and severe groups, respectively, had favorable outcomes. By contrast, 80.8% (21/26) of patients in the critical group had unfavorable outcomes (Fig. 1A). Patients older than 65 years showed more unfavorable than favorable outcomes. Patients with diabetes and body mass index (BMI) of ≥ 30 were more likely to have unfavorable outcomes (Table 1).

Dexzopiclone, a cyclopyrrolone-class drug for insomnia, was administered at a dose of 1.0 mg per day to 82 patients (25.4%) for the duration of their hospitalization. Overall, favorable outcomes were recorded in 77 of these patients and all were discharged (Table 1). Of the five patients receiving hypnotics who had unfavorable outcomes, only 1 died. In comparing hypnotics and non-hypnotics use in patients within the three disease groups, favorable clinical outcomes were more prevalent among patients on hypnotics (94.7% vs. 88.5% for non-severe, 95% vs. 74.6% for severe, and 66.7% vs. 13.0% for critical) ($p < 0.05$) (Fig. 1B). And favorable clinical outcomes were associated with the administration of hypnotics among RT-PCR-positive and RT-PCR-negative patients in each disease severity group (Fig. 1C and 1D).

CT and laboratory abnormalities

The radiologic and laboratory test results are summarized in Table 2 (a complete version is available as Supplementary Table S1). CT abnormalities were found in 314 patients. Ground-glass opacity (GGO) findings were bilateral in 55.0% (83/151), 52.1% (76/146) and 26.9% (7/26) of patients in the non-severe, severe and critical disease groups, respectively. Multiple bilateral pulmonary consolidations and intralocular interstitial thickening were observed more frequently among patients with unfavorable outcomes (11.1%, 7/63) than those with favorable outcomes (0.8%, 2/260). Representative CT images related to clinical outcomes are shown in Fig. S1.

Laboratory findings between patients with favorable and unfavorable outcomes showed differences in leukocyte and neutrophil counts and C-reactive protein, as well as lactate dehydrogenase, creatinine, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, glucose, and serum amyloid A, which were all higher among patients with unfavorable outcomes. Lymphopenia also occurred among 83.6% of patients with unfavorable outcomes, while D-dimer showed no significant differences.

RT-PCR was positive more often among patients in the critical (84.6%) and severe (65.1%) disease groups, than in the non-severe group (45.7%). Patients whose RT-PCR were initially negative also had better clinical outcomes, with only 9.5% (13/137) having unfavorable outcomes.

Treatments and complications

Results related to treatment and complications are shown in Table 3. Oseltamivir (69.7%, 225/323), ganciclovir (71.2%, 230/323), and arbidol (208/323, 64.4%) were the three most frequently used antiviral medications. And one or more courses of moxifloxacin, a broad-spectrum antibiotic, was administered to 94.1% (304/323) of patients. Also, 60.7% (196/323) of patients were given corticosteroid and glucocorticoid, and 95.7% (309/323) received

alternative therapy or traditional Chinese medicine. Kaletra® (lopinavir/ritonavir), an antiretroviral drug for human immunodeficiency virus infection, was more frequently administered to patients in the critical-disease group (46.2%) and in those with unfavorable than favorable outcomes (23.8% vs 5.0%). Interferon- α was also given more often to patients with unfavorable than favorable outcomes (9.5% vs. 6.2%). Other medications showed no significant differences in clinical outcomes.

Oxygen therapy via invasive ventilation and non-invasive ventilation was also given more often to patients with unfavorable clinical outcomes. In comparing the outcome of each treatment within the non-severe or severe or critical disease groups, there was no clear improvement (Fig. S2).

Of the 63 patients with unfavorable outcomes, complications, such as arrhythmia (74.6% vs. 19.6%), acute lung injury (69.8% vs. 21.5%), shock (55.6% vs. 3.1%), acute cardiac injury (33.3% vs. 1.2%), and acute respiratory distress syndrome (20.6% vs. 0%), were significantly more common than in patients with favorable outcomes (Table 3).

Risk factors associated with clinical outcomes and survival analysis

A total of 27 categorical variables were identified in univariate logistic regression analysis, namely: age, smoking, BMI, hypnotics, dyspnea, diabetes, malignancy, cardiovascular and cerebrovascular diseases, serum amyloid A, procalcitonin, hypersensitive troponin I, creatine kinase CMB, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, leukocyte count, neutrophil count, platelet count, RT-PCR at diagnosis, clinical status at admission, bilateral GGO, crazy paving sign, diffuse patchy ground glass and air bronchogram, and multiple bilateral pulmonary consolidation and intralobular interstitial thickening (Table S2). Eight variables were demonstrated as independent risk factors based on the multivariate logistic regression model. The results indicated that age (patients over 65 years) (OR=3.546,

95%CI=1.626–7.733, $p<0.001$), smoking (OR=3.464, 95%CI=1.18–10.166, $p=0.001$), critical disease designation (OR=7.390, 95%CI=2.056–26.569, $p=0.002$), diabetes (OR=3.109, 95%CI=1.155–8.373, $p=0.025$), abnormal higher hypersensitive troponin I (>0.04 pg/mL) (OR=4.388, 95%CI=1.261–15.271, $p=0.02$), white blood cell count ($>10 \times 10^9/L$) (OR=10.853, 95%CI=3.040–38.748, $p<0.001$) and neutrophil count ($>75 \times 10^9/L$) (OR=5.929, 95%CI=2.299–15.290, $p<0.001$) were associated with unfavorable clinical outcome, and hypnotics showed significant protective effects on patient outcomes (OR=0.082, 95%CI=0.025–0.274, $p<0.001$) (Fig. 2A).

Patients in the non-severe group showed significantly better survival compared with those in the severe and critical groups (Fig. 2B). Patients given hypnotics showed significant favorable survival compared with the non-hypnotics (Fig. 2C), and patients with positive RT-PCR results showed significantly poorer survival compared with those with negative RT-PCR (Fig. 2D).

DISCUSSION

In contrast to a previous study,¹² most patients with COVID-19 in the severe group of our series showed favorable clinical outcomes, at approximately the same frequency as in non-severe cases (84.9% vs 86.8%), and survival analysis demonstrated consistently higher survival rates in non-severe and severe cases than in critical cases. Although previous studies failed to show that smoking was a risk factor for COVID-19,^{9,15} multivariate analysis in our study demonstrated that smoking was an independent risk factor for unfavorable outcome. Otherwise, we confirmed findings from other studies^{10,12,14} that age over 65 years and leukocytosis with left shift were associated with poorer clinical outcome.

To our knowledge, this is the first report that dexzopiclone, a commonly prescribed hypnotics drug for insomnia, was significantly associated with improved clinical outcome. Patients of the same disease-severity category, who were administered hypnotics, showed better outcome than those not taking hypnotics. For patients in the more severe disease groups, the improvement effect

was even more pronounced. Also, in analyzing the effect of hypnotics on RT-PCR-positive and RT-PCR-negative patients separately, we found that hypnotics had a more striking effect on the former. Moreover, patients administered hypnotics had a better survival rate.

To further rule out bias, we conducted multivariate analysis (Fig. 2A) to justify other factors. We found that hypnotics were a significant independent factor ($p < 0.001$), and patients using it had better outcomes.

Patients with COVID-19 are typically very anxious and exhibit sleep deficiency and oxygen insufficiency during disease progression, which may lead to the metabolic dysregulation^{19,20} and immune system abnormalities²¹. Better sleep quality and stress reduction could be one justification for prescribing hypnotics to COVID-19 patients. That is, hypnotics could help a patient to overcome difficult and prolonged hospitalization (about 2 to 3 weeks), resulting in improved survival and recovery. Dimitrov and colleagues indicated that sleep can exert some immune-supportive effects and potentially enhance effective T-cell responses.²²

In addition, the superior efficacy of dexzopiclone may be due to enhanced gamma aminobutyric acid (GABA) signaling. That is, dexzopiclone can interact with GABA_A, and GABA_A receptor can magnify responses to GABA.²³ GABA signaling promotes autophagy activation, which improves phagosome maturation and promotes host protection against infections.²⁴ The beneficial effect of hypnotics on COVID-19 clinical outcomes warrants further investigation in the management of COVID-19 patients.

Until now, several descriptive studies have mentioned the ineffectiveness of current medications irrespective of the disease-severity category^{10,12,25}. Our data are in general accord. By specifically comparing the effect of standard treatments for patients in the same disease-severity category (Fig. S2), we were unable to show that any standard therapy could improve clinical outcome. However, since only about 25% of patients in our study were

administered hypnotics, we assume that self-healing could be the major reason for the high recovery rate of patients in the non-severe and severe disease groups. That is, COVID-19 is most likely a self-limited disease in the majority of patients.

Both RT-PCR-confirmed COVID-19 patients and clinically diagnosed patients who were RT-PCR negative were included in this study. Due to the burgeoning epidemic and high exposure situation in Wuhan, the guidelines for COVID-19 diagnosis and treatment indicated that residents of Wuhan with clinical presentations suggestive of COVID-19 (including respiratory symptoms, CT scan results and laboratory tests excluding other infectious causes of pneumonia) could be admitted to hospital irrespective of the RT-PCR result. Actually, all of the RT-PCR-negative patients had CT image features compatible with COVID-19. Moreover, the high false-negativity of RT-PCR (about 20–40%)²⁶ presents a significant burden on health care providers to use their clinical judgment. And chest CT has a higher sensitivity for diagnosis of COVID-19 than RT-PCR.²⁶

Several underlying reasons, including uneven sensitivities of different detection kits, improper collection of throat swab specimens, and low concentration of virus in samples²⁷ can lead to the possible deviation in test results. Therefore, including the RT-PCR-negative patients was an important measure to control and prevent the spread of COVID-19 in Wuhan. We found that patients in the severe or critical disease groups were more likely to be RT-PCR positive. Survival analysis also corroborated that RT-PCR-positive patients showed poorer clinical outcomes.

Since all patients in our study were tested by the same experienced team using the same RT-PCR protocol, we believe the major reason for the negative RT-PCR results in our patient series was due to the low concentration of virus in the throat, which may indicate that patients with negative RT-PCR test might be less likely to infect other people. We found that only a small portion of patients (less than 10%) with negative RT-PCR had unfavorable

outcomes. In performing follow-up RT-PCR on patients in the severe disease group with abnormal CT, we found 23 cases whose first test was negative and later tests were positive. We believe the inclusion of RT-PCR-negative patients with clinically compatible presentation of COVID-19 will help guide clinicians in the care of such patients.

Obesity (BMI ≥ 30), hyperglycemia and diabetes, and cardiovascular disease were distinct risk factors for unfavorable clinical outcomes. Other studies also reported that obesity is associated with worse outcome of COVID-19 patients.^{28,29} Angiotensin-converting enzyme-2 (ACE2), which serves as a cell-entry receptor for SARS CoV-2,³⁰ plays a protective role for both diabetes and cardiovascular diseases.^{31,32} Kuba and colleagues demonstrated that SARS-CoV downregulates ACE2 protein,³³ which could explain why COVID-19 patients with diabetes and cardiovascular disease have worse clinical outcomes.

We found that abnormally high hypersensitive troponin I was an independent predictor for poor clinical outcome. Increased troponin can enhance coagulation activation.³⁴ In patients with COVID-19, immune damage to the hematopoietic system, ischemic hypoxia-reperfusion injury, and drugs can cause coagulation disorders.^{8,34-37} We speculate that increased troponin will induce dysfunction of coagulation and thrombus formation with possible pulmonary embolism, which would further aggravate the patient's condition. D-dimer was found to be very significantly different according to the disease-severity status, and a higher proportion of patients with severe (50.7%) and critical (57.1%) disease had D-dimer levels >0.5 mg/L, which is consistent with other studies^{10,12}. However, in terms of clinical outcomes, even though the patients with unfavorable outcomes had higher percentage (51.9%) of D-dimer >0.5 mg/L than the patients (40.4%) with favorable outcomes, the difference was not statistically significant.

There were some limitations in our study. Incomplete laboratory test results in some patient records may have caused deviations in statistical analysis. Except for hypnotics, we found that all treatments were ineffective and many treatments showed unwanted side effects,

including liver injury.³⁸⁻⁴⁰ Although we did not conduct separate analysis for RT-PCR-positive and RT-PCR-negative patients, our multivariate analysis identified eight independent risk factors, which were independent of the RT-PCR result.

Although the vast majority of patients recovered, approximately 20% of our hospitalized patient cohort had unfavorable clinical outcomes. To what extent chronic respiratory insufficiency or other organ system sequelae occur in COVID-19 patients will require careful and prolonged follow-up studies. So far, it seems there is no effective standard treatment. However, we have found that using hypnotics were significantly associated with improved clinical outcome of COVID-19. We also found that some novel risk factors that could predict patient outcome, which can help in early decision making for improving clinical outcomes of COVID-19 patients.

Contributors

YD, LH, JMW had the idea and initiated the study. LH, HWR, HL, WXY, JL, CS, JJH, CZW, YM, JW, and QBX collected the epidemiological and clinical data. SC, YF, ZG, YZ, ZW and YD processed and conducted statistical data analyses. ZG, YD, RY, YF and SC drafted the manuscript, and all authors revised the manuscript and approved the version for publication. YD is responsible for the integrity of the data and the accuracy of the analyzed data.

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whether to share the data or not based on the research objectives and plan provided. This study was approved by the Ethics Committee of Tianyou Hospital, Affiliated to Wuhan University of Science and Technology (NO202000221).

Oral consent was obtained from patients and written informed consent was waived.

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Declaration of interests

We declare no competing interests.

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Table 1. Demographics and clinical characteristics in disease status and clinical outcome*

Characteristic	Disease severity group				p Value	Clinical outcome		p Value
	All Patients	Non-severe	Severe	Critical		Unfavorable	Favorable	
	323	151	146	26		63	260	
Median Age (years)								
(range)	61(23-91)	56(23-89)	64(23-87)	70(44-91)	<0.001	70(38-91)	58(23-89)	0.736
Age group (years)					<0.001			<0.001
20-40	34/323(10.5)	21/151(13.9)	13/146(8.9)	0/26(0)	0.062	1/63(1.6)	33/260(12.7)	0.006
41-65	178/323(55.1)	97/151(64.2)	70/146(47.9)	11/26(42.3)	0.007	25/63(39.7)	153/260(58.8)	0.009
≥65	111/323(34.4)	33/151(21.9)	63/146(43.2)	15/26(57.7)	<0.001	37/63(58.7)	74/260(28.5)	<0.001
Sex					0.840			0.247
Male	166/323(51.4)	75/151(49.7)	77/146(52.7)	14/26(53.8)	0.840	37/63(58.7)	129/260(49.6)	
Female	157/323(48.6)	76/151(50.3)	69/146(47.3)	12/26(46.2)	0.840	26/63(41.3)	131/260(50.4)	
Occupation								
Employee	98/323(30.3)	63/151(41.7)	34/146(23.3)	1/26(3.8)	<0.001	8/63(12.7)	90/260(34.6)	0.001
Self-Employed	12/323(3.7)	5/151(3.3)	7/146(4.8)	0/26(0)	0.666	0/63(0)	12/260(4.6)	0.133
Retired	144/323(44.6)	61/151(40.4)	59/146(40.4)	24/26(92.3)	<0.001	44/63(69.8)	100/260(38.5)	<0.001

Unemployed	69/323(21.4)	22/151(14.6)	46/146(31.5)	1/26(3.8)	<0.001	11/63(17.5)	58/260(22.3)	0.502
Medical Staff	9/323(2.8)	7/151(4.6)	2/146(1.4)	0/26(0)	0.192	1/63(1.6)	8/260(3.1)	1.000
BMI					0.750			0.017
<25	229/323(70.9)	103/130(79.2)	106/139(76.3)	20/25(80)	0.850	44/56(78.6)	185/238(77.7)	1.000
25-30	52/323(16.1)	22/130(16.9)	27/139(19.4)	3/25(12)	0.718	6/56(10.7)	46/238(19.3)	0.185
≥30	13/323(4)	5/130(3.8)	6/139(4.3)	2/25(8)	0.522	6/56(10.7)	7/238(2.9)	0.029
Onset time–Median (range)	9(1-60)	8.5(1-30)	10(1-60)	8.5(2-20)	0.093	9(1-28)	9(1-60)	0.021
Hypnotics					<0.001			<0.001
Yes	82/323(25.4)	19/132(14.4)	60/127(47.2)	3/26(11.5)	<0.001	5/55(9.1)	77/230(33.5)	
No	203/323(62.8)	113/132(85.6)	67/127(52.8)	23/26(88.5)	<0.001	50/55(90.9)	153/230(66.5)	
Temperature (°C)								
≤37.00	133/323(41.1)	63/150(42)	65/146(44.5)	5/26(19.2)	0.049	26/63(41.3)	107/259(41.3)	1.000
37.01-38.00	105/323(32.5)	43/150(28.7)	54/146(36.9)	8/26(30.7)	0.305	16/63(25.4)	89/259(34.4)	0.226
38.01-39.00	67/323(20.7)	34/150(22.7)	24/146(16.4)	9/26(34.6)	0.081	15/63(23.8)	52/259(20.1)	0.630
≥39.01	17/323(5.3)	10/150(6.7)	3/146(2.1)	4/26(15.4)	0.011	6/63(9.5)	11/259(4.2)	0.172
Smoking history					0.123			0.045
Yes	38/323(11.8)	12/151(7.9)	22/146(15.1)	4/26(15.4)	0.123	12/63(19)	26/260(10)	
No	285/323(88.2)	139/151(92.1)	124/146(84.9)	22/26(84.6)	0.123	51/63(81)	234/260(90)	
Drinking					0.078			0.816

Yes	36/323(11.1)	18/151(11.9)	12/146(8.2)	6/26(23.1)	0.078	6/63(9.5)	30/260(11.5)	
No	287/323(88.9)	133/151(88.1)	134/146(91.8)	20/26(76.9)	0.078	57/63(90.5)	230/260(88.5)	
Signs and symptoms								
Fever	271/323(83.9)	130/151(86.1)	121/146(82.9)	20/26(76.9)	0.452	51/63(81)	220/260(84.6)	0.604
Cough	164/323(50.8)	74/151(49)	77/146(52.7)	13/26(50)	0.810	34/63(54)	130/260(50)	0.671
Fever and cough	244/323(75.5)	100/151(66.2)	127/146(87)	17/26(65.4)	<0.001	46/63(73)	198/260(76.2)	0.721
Chest distress	3/323(0.9)	0/151(0)	2/146(1.4)	1/26(3.8)	0.067	2/63(3.2)	1/260(0.4)	0.098
Nausea and vomiting	1/323(0.3)	0/151(0)	0/146(0)	1/26(3.8)	0.080	1/63(1.6)	0/260(0)	0.195
Dyspnea	14/323(4.3)	6/151(4)	6/146(4.1)	2/26(7.7)	0.537	6/63(9.5)	8/260(3.1)	0.056
Shivering	1/323(0.3)	1/151(0.7)	0/146(0)	0/26(0)	1.000	0/63(0)	1/260(0.4)	1.000
Headache	3/323(0.9)	3/151(2)	0/146(0)	0/26(0)	0.313	0/63(0)	3/260(1.2)	1.000
Chronic medical illness/coexisting conditions								
Cirrhosis	3/323(0.9)	3/151(2)	0/146(0)	0/26(0)	0.313	0/63(0)	3/260(1.2)	1.000
Hypertension	105/323(32.5)	39/151(25.8)	56/146(38.4)	10/26(38.5)	0.056	27/63(42.9)	78/260(30)	0.071
Diabetes	47/323(14.6)	14/151(9.3)	22/146(15.1)	11/26(42.3)	<0.001	19/63(30.2)	28/260(10.8)	<0.001
Malignancy	5/323(1.5)	0/151(0)	4/146(2.7)	1/26(3.8)	0.033	3/63(4.8)	2/260(0.8)	0.053
Cerebrovascular disease	7/323(2.2)	4/151(2.6)	3/146(2.1)	0/26(0)	1.000	2/63(3.2)	5/260(1.9)	0.626
COPD†	6/323(1.9)	0/151(0)	5/146(3.4)	1/26(3.8)	0.033	2/63(3.2)	4/260(1.5)	0.332

Chronic kidney disease	7/323(2.2)	4/151(2.6)	3/146(2.1)	0/26(0)	1.000	0/63(0)	7/260(2.7)	0.353
Chronic liver disease	5/323(1.5)	3/151(2)	2/146(1.4)	0/26(0)	1.000	0/63(0)	5/260(1.9)	0.587
Cardiovascular and cerebrovascular diseases	41/323(12.7)	8/151(5.3)	22/146(15.1)	11/26(42.3)	<0.001	13/63(20.6)	28/260(10.8)	0.057
Digestive system disease	22/323(6.8)	8/151(5.3)	10/146(6.8)	4/26(15.4)	0.158	7/63(11.1)	15/260(5.8)	0.218
Endocrine system disease	15/323(4.6)	4/151(2.6)	10/146(6.8)	1/26(3.8)	0.219	4/63(6.3)	11/260(4.2)	0.504
Nervous system disease	10/323(3.1)	5/151(3.3)	3/146(2.1)	2/26(7.7)	0.258	4/63(6.3)	6/260(2.3)	0.109
Respiratory system disease	29/323(9)	8/151(5.3)	15/146(10.3)	6/26(23.1)	0.010	9/63(14.3)	20/260(7.7)	0.162

*The clinical outcome was categorized into unfavorable and favorable. Unfavorable: patients died, or the condition was getting worse. Favorable: patients discharged, or condition improved.

†COPD; Chronic obstructive pulmonary disease

Table 2. Radiographic and laboratory findings of 323 patients with COVID-19 (Part of Table S2)

[illegible]

≤3	30/323(9.3)	13/141(9.2)	17/139(12.2)	0/26(0)	0.143	0/60(0)	30/246(12.2)	
>3	276/323(85.4)	128/141(90.8)	122/139(87.8)	26/26(100)	0.143	60/60(100)	216/246(87.8)	
Serum amyloid A, > 10 mg/L	35/323(10.8)	14/136(10.3)	21/133(15.8)	0/23(0)	0.06	1/55(1.8)	34/237(14.3)	0.006
Hypersensitive troponin I, > 0.04 pg/mL	68/323(21.1)	21/100(21)	41/123(33.3)	6/21(28.6)	0.144	19/49(38.7)	49/195(25.1)	0.084
Prothrombin time, >14 s	39/323(12.1)	9/124(7.3)	24/137(17.5)	6/26(23.1)	0.018	13/56(23.2)	26/231(11.3)	0.034
Creatine kinase–CMB, U/L †								0.007
≤5	49/323(15.2)	14/41(34.1)	33/47(70.2)	2/11(18.2)	<0.001	5/22(22.7)	44/77(57.1)	
>5	50/323(15.5)	27/41(65.9)	14/47(29.8)	9/11(81.8)	<0.001	17/22(77.3)	33/77(42.9)	
Lactate dehydrogenase, U/L †								
<120	46/323(14.2)	14/38(36.8)	30/42(71.4)	2/7(28.6)	0.002	4/15(26.7)	42/72(58.3)	0.044
>250	22/323(6.8)	12/38(31.6)	6/42(14.3)	4/7(57.1)	0.028	9/15(60)	13/72(18.1)	0.002
Alanine aminotransferase, U/L								
<7	44/323(13.6)	14/145(9.7)	30/143(21)	0/25(0)	0.002	3/62(4.8)	41/251(16.3)	0.023
>40	58/323(18)	26/145(17.9)	24/143(16.8)	8/25(32)	0.189	19/62(30.6)	39/251(15.5)	0.01
Aspartate aminotransferase, U/L								
<13	49/323(15.2)	14/145(9.7)	33/144(22.9)	2/25(8)	0.004	4/62(6.5)	45/252(17.9)	0.03
>35	89/323(27.6)	33/145(22.8)	40/144(27.8)	16/25(64)	<0.001	32/62(51.6)	57/252(22.6)	<0.001
Blood urea nitrogen, >8 mmol/L	72/323(22.3)	18/145(12.4)	46/142(32.4)	8/25(32)	<0.001	22/61(36.1)	50/251(19.9)	0.012

Creatinine, $\mu\text{mol/L}$

<88	269/323(83.3)	128/145(88.3)	120/144(83.3)	21/25(84)	0.452	46/62(74.2)	223/252(88.5)	0.007
>144	7/323(2.2)	2/145(1.4)	4/144(2.8)	1/25(4)	0.321	4/62(6.5)	3/252(1.2)	0.03

Glucose, mmol/L

<3.9	43/323(13.3)	14/137(10.2)	29/143(20.3)	0/21(0)	0.007	2/59(3.4)	41/242(16.9)	0.006
>6.1	108/323(33.4)	38/137(27.7)	52/143(36.4)	18/21(85.7)	<0.001	38/59(64.4)	70/242(28.9)	<0.001

RT-PCR

Positive	186/323(57.6)	69/151(45.7)	95/146(65.1)	22/26(84.6)	<0.001	50/63(79.4)	136/260(52.3)	<0.001
Negative	137/323(42.4)	82/151(54.3)	51/146(34.9)	4/26(15.4)	<0.001	13/63(20.6)	124/260(47.7)	

†Data were missing for creatine kinase in 226 (69.5%) and for lactate dehydrogenase in 238 (73.2%) patients.

Table 3. Treatments, complications, and clinical outcome

	All Patients	Disease severity group			p Value	Clinical outcome		p Value
		Non-severe	Severe	Critical		Unfavorable	Favorable	
	323	151	146	26		63	260	
Treatment								
Antiviral therapy								
Oseltamivir	225/323(69.7)	109/151(72.2)	97/146(66.4)	19/26(73.1)	0.518	47/63(74.6)	178/260(68.5)	0.425

Ganciclovir	230/323(71.2)	113/151(74.8)	99/146(67.8)	18/26(69.2)	0.398	42/63(66.7)	188/260(72.3)	0.464
Arbidol	208/323(64.4)	99/151(65.6)	95/146(65.1)	14/26(53.8)	0.501	45/63(71.4)	163/260(62.7)	0.249
Kaletra	28/323(8.7)	5/151(3.3)	11/146(7.5)	12/26(46.2)	<0.001	15/63(23.8)	13/260(5)	<0.001
Interferon- α	22/323(6.8)	8/151(5.3)	8/146(5.5)	6/26(23.1)	0.003	6/63(9.5)	16/260(6.2)	0.500
Antibiotic therapy								
Antibiotics	304/323(94.1)	143/151(94.7)	137/146(93.8)	24/26(92.3)	0.764	62/63(98.4)	242/260(93.1)	0.139
Steroid therapy								
Corticosteroid/glucocorticoid	196/323(60.7)	87/151(57.6)	86/146(58.9)	23/26(88.5)	0.007	54/63(85.7)	142/260(54.6)	<0.001
Continuous renal replacement therapy								
	72/323(22.3)	26/151(17.2)	42/146(28.8)	4/26(15.4)	0.048	10/63(15.9)	62/260(23.8)	0.232
Alternative therapy								
	309/323(95.7)	139/151(92.1)	145/146(99.3)	25/26(96.2)	0.005	62/63(98.4)	247/260(95)	0.319
Oxygen support								
Non-invasive ventilation	105/323(32.5)	29/151(19.2)	60/146(41.1)	16/26(61.5)	<0.001	35/63(55.6)	70/260(26.9)	<0.001
Invasive ventilation	34/323(10.5)	2/151(1.3)	13/146(8.9)	19/26(73.1)	<0.001	33/63(52.4)	1/260(0.4)	<0.001
Complication								
Shock	43/323(13.3)	4/151(2.6)	23/146(15.8)	16/26(61.5)	<0.001	35/63(55.6)	8/260(3.1)	<0.001
Acute cardiac injury	24/323(7.4)	2/151(1.3)	9/146(6.2)	13/26(50)	<0.001	21/63(33.3)	3/260(1.2)	<0.001
Arrhythmia	98/323(30.3)	18/151(11.9)	55/146(37.7)	25/26(96.2)	<0.001	47/63(74.6)	51/260(19.6)	<0.001
ARDS*	13/323(4)	1/151(0.7)	4/146(2.7)	8/26(30.8)	<0.001	13/63(20.6)	0/260(0)	<0.001

Acute kidney injury	17/323(5.3)	2/151(1.3)	5/146(3.4)	10/26(38.5)	<0.001	14/63(22.2)	3/260(1.2)	<0.001
Acute respiratory injury	100/323(31)	13/151(8.6)	65/146(44.5)	22/26(84.6)	<0.001	44/63(69.8)	56/260(21.5)	<0.001
Septic shock	19/323(5.9)	0/151(0)	2/146(1.4)	17/26(65.4)	<0.001	19/63(30.2)	0/260(0)	<0.001
Secondary infection	9/323(2.8)	1/151(0.7)	4/146(2.7)	4/26(15.4)	0.002	9/63(14.3)	0/260(0)	<0.001

*ARDS, Acute respiratory distress syndrome

Figure legends

Figure 1. Clinical outcomes for the three disease severity groups.

(A) Overall clinical outcomes of patients in the non-severe, severe, and critical disease groups. The percentages are calculated by the number of each outcome group (Unfavorable or Favorable) divided by the total number of patients in each group. (B) Clinical outcomes of patients in the non-severe, severe, and critical disease groups who were either administered hypnotics or not. (C) Clinical outcomes of RT-PCR-positive patients in the non-severe, severe, and critical disease groups who were either administered hypnotics or not. (D) Clinical outcomes of RT-PCR-negative patients in the non-severe, severe, and critical disease groups who were either administered hypnotics or not. The percentages are calculated by the number of each outcome group (Unfavorable or Favorable) divided by the total number at each diagnosis status with either using (Yes) or not using (No) hypnotics.

Figure 2. Multivariate regression and Kaplan-Meier curves of survival analysis.

(A) Factors showing significantly independent association with clinical outcome. Odds ratio, 95%CI, and P values are derived from logistic regression modelling. (B) Kaplan-Meier curve demonstrating survival of COVID-19 patients by disease severity group: non-severe, severe, and critical. (C) Kaplan-Meier curve demonstrating survival of COVID-19 patients by the usage of hypnotics. (D) Kaplan-Meier curve demonstrating survival of COVID-19 patients by RT-PCR results. P values for survival analysis are derived by the log-rank test.

Figure 1

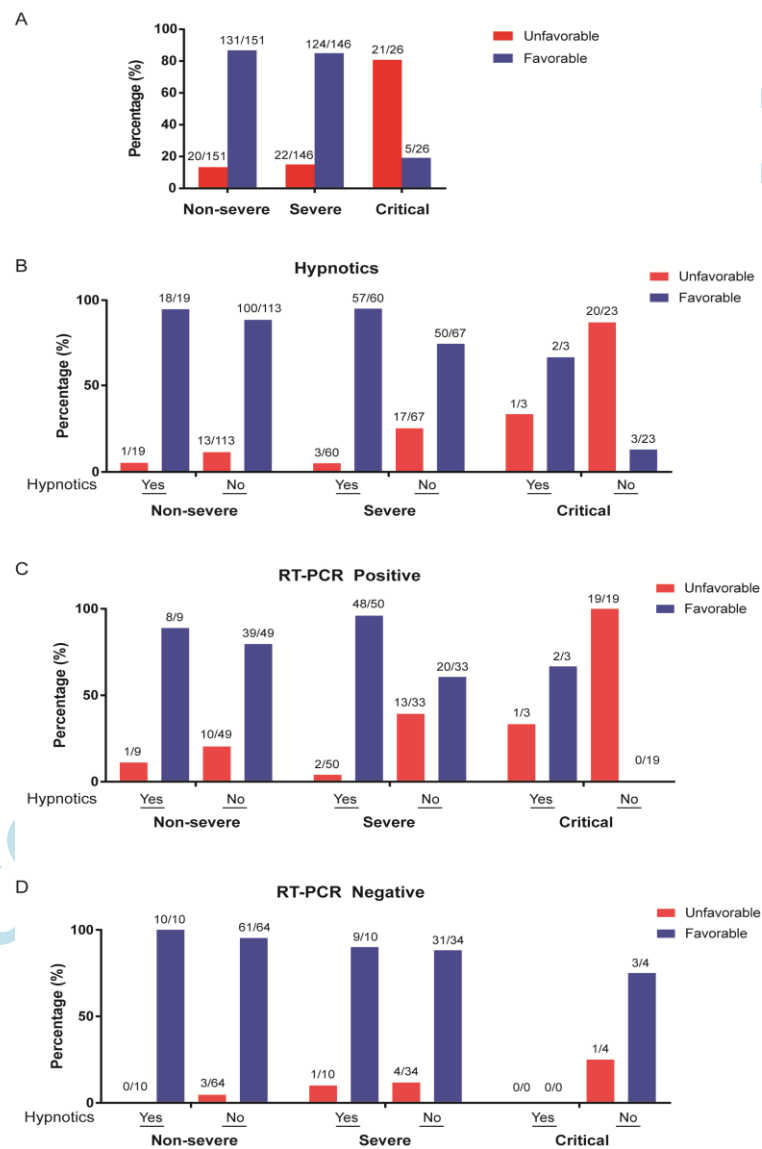
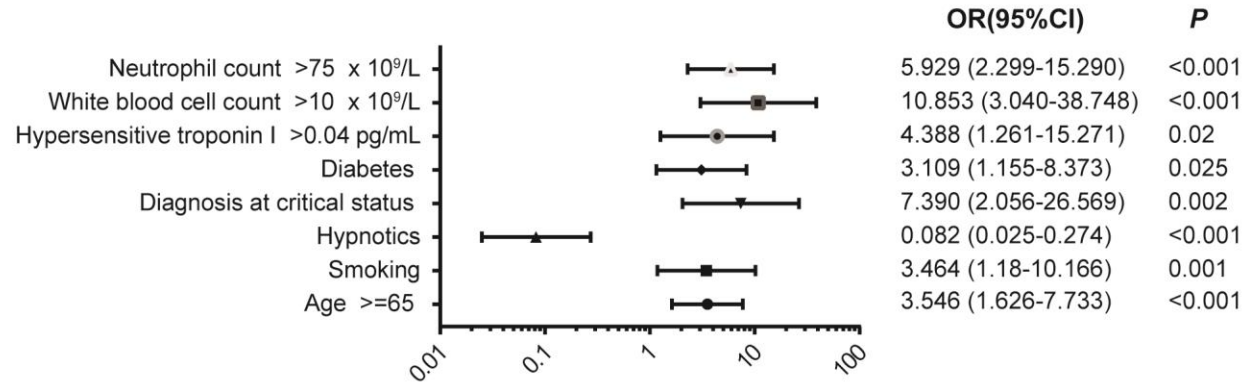
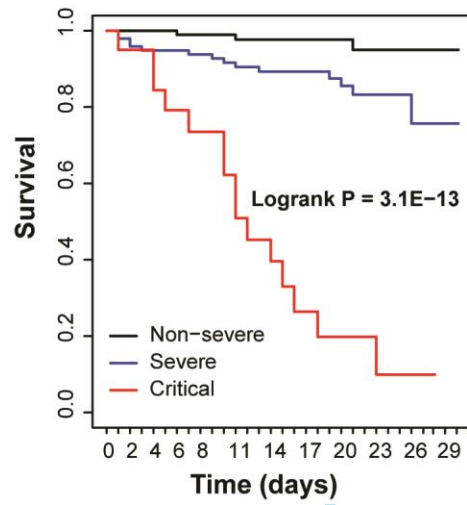


Figure 2

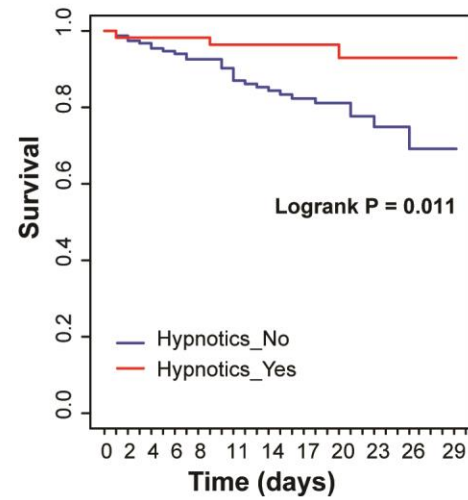
A



B



C



D

