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Association of consciousness impairment and mortality in people with COVID-19

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Abstract

Background

To investigate the association between impairment of consciousness and risk of death in people with COVID-19.

Methods

In this multicentre retrospective study, we enrolled people with confirmed COVID-19 from 44 hospitals in Wuhan and Sichuan, China, between 18 January and 30 March 2020. We extracted demographics, clinical, laboratory data and consciousness level (as measured by the Glasgow Coma Scale (GCS) score) from medical records. We used Cox proportional hazards regression, structural equation modelling and survival time analysis to compare people with different progressions of impaired consciousness.

Results

We enrolled 1,143 people (average age 51.3 ± standard deviation 17.1-year-old; 50.3% males), of whom 76 died. Increased mortality risk was identified in people with GCS score between 9 and 14 (hazard ratio (HR) 46.76, P<0.001) and below 9 (HR 65.86, P<0.001). Pathway analysis suggested a significant direct association between consciousness level and

death. Other factors including age, oxygen saturation level and pH had indirect associations with death mediated by GCS scores. People who developed impaired consciousness more rapidly either from symptoms onset (<10 days vs 10-19 days, p=0.025, <10 days vs ≥ 20 days and 10-19 days vs ≥20 days, <0.001) or deterioration of oxygen saturation (≤ 2 days vs> 2 days, p=0.028) had shorter survival times.

Conclusion

Altered consciousness and its progression had a direct link with death in COVID-19. Interactions with age, oxygen saturation level, and pH suggest possible pathophysiology. Further work to confirm these findings, explore prevention strategies and interventions to decrease mortality is warranted.

Keywords: outcomes; risk factors; death; Glasgow Coma Scale

Introduction

COVID-19, caused by a novel coronavirus (SARS-CoV-2), is a severe acute respiratory syndrome first reported in Wuhan, China, in December 2019[1]. It evolved rapidly into a global pandemic[2]. The main clinical presentations include fever, cough and shortness of breath; copious sputum production and haemoptysis and other non-specific symptoms are also seen[3]. Critical neurological events, including impairment of consciousness and cerebrovascular accidents have been reported[4-8]. Impairment of consciousness is one of the most typical neurological manifestations, especially in severe, often-fatal conditions. One study reported that altered consciousness at admission was a predictor for developing critical illness[9]. It has also been reported that older age, male sex, and the presence of comorbidities were risk factors of higher mortality[10,11]. Reports of the association of consciousness impairment during the illness course and outcomes are lacking, as levels and progression of altered consciousness have not been fully evaluated previously.

We aimed to investigate the associations between altered consciousness with differing time courses and death in COVID-19 and to estimate the possible causality of key clinical variables and consciousness levels on mortality.

Methods

Ethics

The Ethics Board of West China Hospital, Sichuan University (approval 2020[100])

approved the study. The Committed waived the need for informed consent due to the circumstances, and retrospective nature of the study and the confirmation of full anonymization of data.

Recruitment

Forty-four hospitals officially designated as COVID-19 treating centres from Wuhan (Hubei Province) and Sichuan Province, China, participated. Consecutive people admitted to these hospitals who met COVID-19 diagnostic criteria according to the National Guidelines (Trial Version 6)[12] were enrolled. Briefly, the diagnosis was confirmed by the presence of the typical symptoms and/or characteristic features on chest imaging together with positive testing for SARS-CoV-2 RNA by real-time polymerase chain reaction (PCR). Enrolment was between 18 January and 20 March 2020 in Sichuan and extended to 30 March in Wuhan. Among them, 223 people discharged before 18 February have been previously reviewed for seizure-related events[13], and 741 enrolled before 20 March were reviewed for new-onset neurologic events[14]. Recruitment flow is shown in Additional file 1: Fig S1. Those who tested negative and those with insufficient information for the evaluation of consciousness levels were excluded.

Clinical data collecting

A standardized clinical report form was designed to extract data from medical records retrospectively (https://www.wjx.cn/jq/85385510.aspx). Demographics and related

clinical features were collected. According to National Guidelines [12], each participant's clinical condition was classified as mild, moderate, severe or critical. People with symptoms but no signs of pneumonia on imaging were considered "mild", while those with symptoms and pneumonia signs were classified as "moderate". Criteria for a severe condition were respiratory distress with respiration rate (RR) ≥ 30/min, resting oxygen saturation ≤ 93% and PaO2 / FiO2 ≤ 300 mmHg. People with respiratory failure, shock or other organ failure requiring intensive care unit (ICU) admission were considered critical. Two neurologists using the Glasgow Coma Scale (GCS) independently estimated consciousness levels when altered consciousness was first mentioned in the medical notes. In cases of inconsistent scores, case-notes were reviewed, and a third physician or neurologist settled the scores. For people on ventilators or with language disability, the verbal response was evaluated as "1" [15]. In those sedated, GCS scores were estimated before the introduction of sedatives. Blood oxygen saturation was recorded from the pulse oximeter if no blood gas assay was performed. Blood pH was taken from the blood gas assay. In people with GCS <15, oxygen saturation levels and pH were recorded during disturbed consciousness or the lowest recording during admission if a corresponding oxygen level was not available. For those fully conscious throughout the admission, the lowest oxygen saturation was recorded. Outcomes were discharge, death or continued hospitalization, for those we didn't have the outcome at the study end. We recorded dates of first symptoms, admission, discharge, death or last entry date if still in the hospital. The date of the first record of impaired consciousness was recorded. Time at respiratory deterioration,

defined as when oxygen saturation <95% was first noted, was recorded.

Grouping and data processing

Participants were categorized into 3 subgroups according to GCS scores: 1) GCS = 15; 2) between 14 and 9; and 3) < 9. In people with mild or moderate illness, with no record of respiratory dysfunction and who never had blood gas assay, pH values were taken as 7.40. The original blood pH value was converted into the absolute value of the deviation from normal (7.35 to 7.45) for further analysis. For those whose pH value fell within this interval, pH was considered as "0" in this conversion.

Statistical analysis

Data analysis was performed using STATA 16.0 (StataCorp LLC, Texas, USA), MPLUS 8.3 (Muthén & Muthén, California, USA) and statistical significance was set at P<0.05. Frequencies and percentages were used to describe the cohort and GCS sub-groups. We excluded cases in the corresponding analysis if any variable involved was missing.

Cox proportional hazards regression modelling was used to assess the effect of GCS scores on death risk, adjusting for potential confounders (age, gender, smoking, acute complications, medical history, COVID-19 severity, oxygen saturation level and blood pH). The proportional hazards assumption was tested using Schoenfeld residuals. People with missing survival time were excluded in the Cox regression modelling. The

survival time was estimated from the time of symptom onset in all data analysis.

We used structural equation modelling to assess the interrelationships of key variables to death. Age, oxygen saturation level and pH were used as continuous variables. Parameters were estimated using the robust weighted least squares (WLSMV) method and 1,000 bootstrapping procedure were performed to obtain the bias-corrected 95% confidence interval (CI) of the indirect effect. We excluded people with an uncertain outcome (still in hospital at study-end) from the equation model.

We analyzed the time effect of the disturbance of consciousness in those with altered GCS scores using a Kaplan-Meier survival curve. First, we estimated progression from altered consciousness to death. Participants were divided into three groups according to the time from onset of COVID-19 symptoms to the first evidence of impaired consciousness as: 1) < 10 days; 2) between 10 to 19 days and 3) ≥ 20 days. Next, based on the time from the first reduction of blood oxygen saturation to 95% or below to first evidence of altered consciousness, individuals were classified into two groups, ≤ 2 days and > 2 days. Results of the log-rank test are presented to compare the survival status between the groups intuitively. Median survival time and hazard ratio were estimated.

Results

We enrolled 1,143 individuals with an overall mortality of 6.6% (76/1143). Additional

file 2: Table S1 provides a list of participating hospitals with inclusion numbers. The average age was 51.26 years (standard deviation of 17.08 years), 574 were men (50.3%). In Wuhan 670 people were enrolled, and 73 (10.9%) of them died in hospital. The remaining 473 cases were from Sichuan with 3 (0.6%) in-hospital deaths reported. The workflow of data analysis is shown in Additional file 1: Fig S1. Eight-four reported disturbance of consciousness during admission, of whom 53 had a GCS score < 9. Demographics and GCS subgroups are listed in Additional file 3: Table S2. The most frequent co-morbidities recorded were hypertension (n=260), diabetes (n=115) and cardiovascular disease (n=90). Acute complications were listed in Additional file 4: Table S3, and the commonest acute complications were electrolyte disturbance (n=161), hepatic insufficiency(n=138), anaemia (n=119) and type I respiratory failure (n=99). No individual comorbidities or complications were significant in the regression model (data not shown). Thus, they were merged into combined factors referred to as 'Acute complication' and 'Comorbidities' in the following regression analysis. Computed tomography (CT) brain scans were performed in 26 individuals of whom eight had abnormalities, details have been previously published[5].

Risk factors for mortality during hospitalization

We included 799 participants in the multivariable Cox regression, of whom 54 died (Table 1). The only significant risk factor was the GCS; both groups with GCS <15 were significantly more at risk of death than the group with GCS 15, ($p<0.001$). The hazard ratio was 46.76 for those with GCS between 9 and 14 and 65.86 for those with

score < 9, compared to those with normal GCS score. The effect of other risk factors, including age, gender, current smoker, acute complications, medical history, and the severity of COVID-19 was not significant in the multivariable regression.

The pathway analysis among key factors of mortality

To assess the association between impairment of consciousness and death and potential mechanisms, we employed structural equation modelling using four key predictors: age, oxygen saturation level, pH deviation and GCS score. We excluded 144 people still in hospital at study-end from this analysis. Based on the 776 participants (Figure 1) the model suggested a significant direct link between GCS score and death. The three other factors each showed significant indirect associations with death through GCS, with no significant direct associations.

Time course from altered consciousness to death

We first evaluated time from COVID-19 onset to consciousness impairment. Eighty-four individuals with altered GCS score were divided into three groups based on the time span: 1) < 10 days: 13 people of whom 12 died by the study end; 2) between 10 to 19 days: 46 people of whom 39 died and 3) ≥ 20 days: 25 people of whom 19 died; the median (quartile) time interval between the symptom onset to the consciousness impairment was 14 (11, 22) days. Survival was significantly different among groups (log-rank tests: <10 days vs 10-19 days, p=0.025; <10 days vs ≥20 days and 10-19 days vs ≥20 days, p<0.001, shown in Figure 2). We then evaluated whether the rapid

development of consciousness alteration after the deterioration of oxygen saturation was also a significant predictive factor (shown in Figure 3). Five people who never had a record of an oxygen saturation < 95% were excluded, the remaining 79 people were divided into two groups 1) ≤ 2 days: 44 people in which 38 died; 2) > 2 days: 35 in which 29 died. Survival time was significantly different between those who developed consciousness alteration within and beyond 2 days after the deterioration of oxygen saturation (p=0.028). The median survival time and HR of the groups in the time course analysis are provided in Table 2, with significant differences in all comparisons.

Discussion

We assessed levels of consciousness and their association with risk of fatality. GCS scores were the only factor associated with death in the Cox regression model. The structural equation modelling confirmed this. Other critical factors such as age, oxygen saturation level and pH were indirectly associated with death but mediated by GCS scores. Survival analysis suggested that early impairment of consciousness during the course or after hypoxemia led to a shorter survival time and higher mortality.

The COVID-19 mortality rate varies depending on location and populations assessed[16,17]. COVID-19 may occur in healthy individuals of any age and most will have a mild condition. Several reports have provided various risk factors for COVID-10 related death, including older age, smoking, male sex, comorbidities, and elevated d-dimer[11,18,19]. Current evidence of the impact of altered consciousness on mortality is

scarce. One study suggested unconsciousness is an independent predictive factor of developing critical illness[20].

Assessing the association between consciousness and mortality is challenging, as consciousness is a dynamic process with many potential confounders. We designed a retrospective assessment and systematically reviewed our cohort. We focused on timing, oxygen saturation and pH when impairment of consciousness was first noticed. We also applied structural equation modelling, a robust technique to assess complex, dynamic and multivariable relationships, after the traditional regression model to confirm and explore its result. In the structural equation modelling, multi-equations are formulated, and variables do not have a clear dependent and independent distinction when compared to regression modelling, as a dependent variable in one model might be an independent variable in another equation[21]. This enables the method, to some extent, to infer causal relationships[22]. It has been widely used to analyze complex associations in different areas including medicine, particularly to explore aetiology and identify best treatments[23,24].

Our findings suggest that COVID-19 deaths are mainly associated with lower GCS scores. In the structural equation modelling, other factors such as age, oxygen saturation and pH played an indirect role mediated by a lower GCS score. Death in COVID-19 seems likely mediated by the decreased consciousness and indirectly associated with age, oxygen saturation, and pH value. Time to event analysis

suggested a rapid development of consciousness disorders either from COVID-19 onset or the deterioration of oxygen saturation had a significant impact on the median survival time. It also indicated that death was likely a consequence of decreased blood oxygen level mediated by a lower GCS score.

Conversely, low tolerance to hypoxia could also lead to a shorter expectation of survival time. Further work is warranted to identify the causes of impaired consciousness and efficacious, cost-efficient treatment. One explanation of the rapid hypoxia is a cytokine storm thought to play an essential role in developing critical illness or death. It is characterized by the onset of overwhelming systemic inflammation, hyperferritinemia, hemodynamic instability, and multi-organ failure. The increased production of pro-inflammatory cytokines could also lead to acute respiratory distress syndrome[25].

Several studies have shown that disorders of consciousness occur commonly in older people with severe conditions [6,14,26]. The causes of altered consciousness in people with COVID-19 have not yet been fully understood. They are, however, likely linked to hypoxemia or brain viremia[14], which may cause a toxic encephalopathy, and this has been supported by some post-mortem studies[27]. Central respiratory failure caused by brainstem insults has been challenged by negative post-mortem brainstem findings[28]. This is also in agreement with our findings that poor outcomes were indirectly associated with lower oxygen levels and altered blood pH, mediated by consciousness impairment. A few case reports of electroencephalogram findings in unconscious

people suggested a pattern compatible with either a direct viral insult to the brain, or demyelination and inflammatory lesions secondary to cytokine storm as a post-viral autoimmune process[29,30]. Cases with encephalitis with or without SARS-CoV-2 identified in cerebrospinal fluid have been reported[7,31], but evidence of a direct insult to the brain is still lacking[32]. Decreased consciousness levels have also been reported in people with large hemispheric infarction and reversible encephalopathy syndrome suggesting brain endothelial dysfunction[33]. Understanding the different causes of disturbed consciousness is crucial as it may lead to distinctive treatment. During the early outbreak, with health systems under significant challenges, a higher proportion of people becoming unconscious and deaths were noted in Hubei than in other parts of China[34]. This is consistent with our findings that altered consciousness is the "red flag" for death which should be noted and trigger early intervention. Establishing consciousness levels requires dynamic re-evaluation, to avoid missing early signs of deterioration.

SARS-COV-2 seems to be associated with more consciousness impairment than other coronaviruses. One report concerning the Middle East respiratory syndrome CoV (MERS-CoV) identified a much higher proportion of people with confusion than in our cohort[35]. Different design and population may account for the divergent results between our study and others.

Our study has limitations: Firstly, we only included individuals with enough information,

but the retrospective nature decreases the power of evidence by the inevitability of missing data. For example, not all patients with neurological impairment performed CT scans. Moreover, new methods should also be used to fill missing components, such as when scoring the verbal response in ventilated individuals[36]. Secondly, some individuals were still in-hospital at the study-end, which might influence the results. Thirdly, we cannot infer definite causality, regardless of how well the association presented by the regression model and the structural equation model explained the data. Fourthly, GCS is not sensitive in detecting altered mental states such as delirium or psychosis; we tried to minimize the uncertainty by using categorical instead of continuous data. GCS scores were assessed independently by at least two neurologists with contradictory scores resolved by a third senior reviewer.

Conclusion

Despite these limitations, our findings suggested a direct link between consciousness impairment and death in COVID-19. Future work assessing consciousness level and correlation with illness severity and death in larger cohorts are needed, along with optimal assessment tools and treatment to decrease COVID-19 mortality.

Declarations

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Consent for Publication

Not applicable

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Availability of Data and Materials

Reasonable requests from any qualified investigator is required for the sharing of anonymized data.

Authors' Contributions

WX, LL, JM, CZ and DZ designed the study protocol and the questionnaire. WX, LL and BZ conceived of the analysis. WX, LL and BZ conducted the analysis and wrote the first draft of the manuscript with feedback from all other authors. JL, ML and LH were involved in collecting and managing data. JWS revised the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The Ethics Board of West China Hospital, Sichuan University (approval 2020[100]) approved the study. The Committed waived the need for informed consent due to the circumstances, and retrospective nature of the study and the confirmation of full anonymization of data.

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Figure legends

Figure 1. Pathway analysis model among GCS scores, SpO_2 and pH deviation

GCS: Glasgow Coma Scale. * p<0.05

All four key variables were used in the structural equation modelling, the presentation has been simplified to highlight the direct and indirect pathways to death among two variables.

Solid lines represent direct associations, while the dotted lines represent indirect pathways. Numbers showed are standardized coefficients (standard error) for each structural equation modelling. For direct pathway, the t values are the result of the standardized coefficients divided by the standard error. The p values of the associations reach the significance level of 0.05 when t is greater than 1.96 (or less than - 1.96). Positive and negative values of the indirect coefficients show the direction of association.

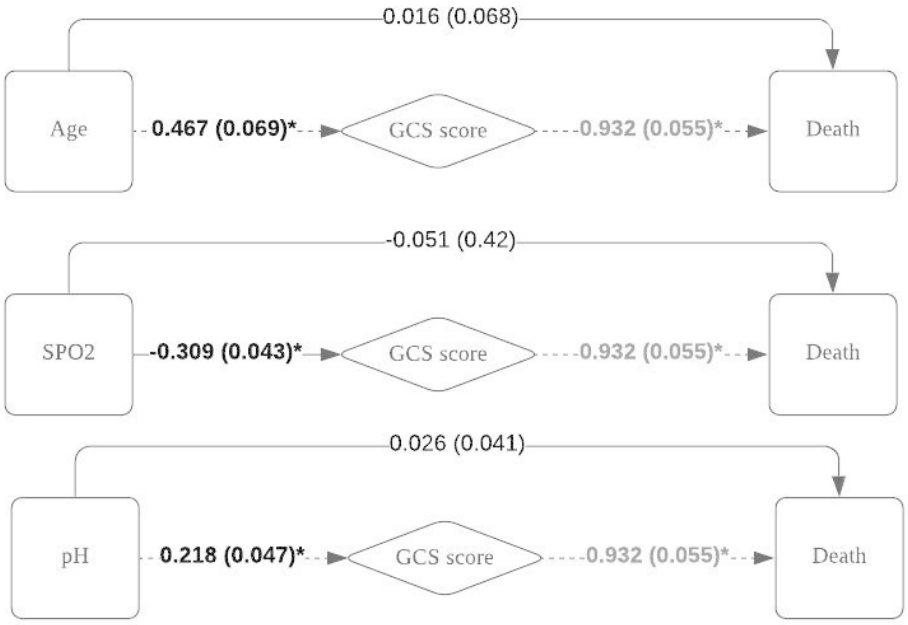
For indirect pathways (mediating pathways), the coefficients were the product of the coefficients of the direct pathway. The coefficients and confidence intervals of these three mediating pathways were: age→ GCS → Death, 0.435 (95% CI 0.296, 0.593); SpO2→ GCS → Death, -0.288 (95% CI -0.379, -0.211); and pH → GCS → Death, 0.203 (95% CI 0.125, 0.297).

Figure 2. Kaplan-Meier survival Curve among individuals who had altered consciousness with different speeds of progression during the illness course

Figure 3. Kaplan-Meier survival Curve among individuals who had blood oxygen saturation deterioration with different speeds of progression during the illness course.

Additional files

Additional File 1-4: Figure S1, Tables S1-S3. Fig S1. - [flowchart of the study]. TableS1- [Participating hospital list]. TableS2- [Demographic and clinical features]. TableS3- [Acute complications]



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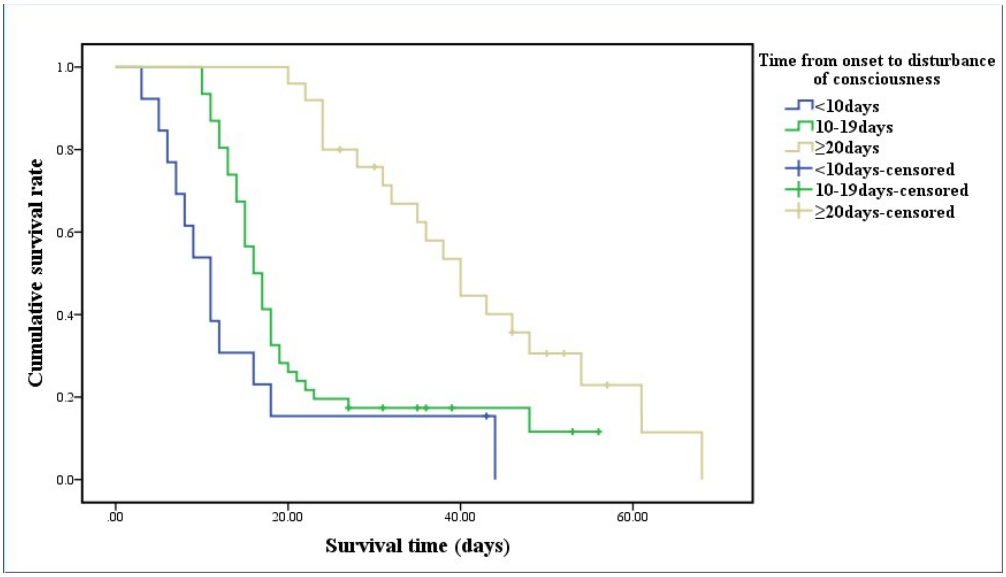

229x130mm (96 x 96 DPI)

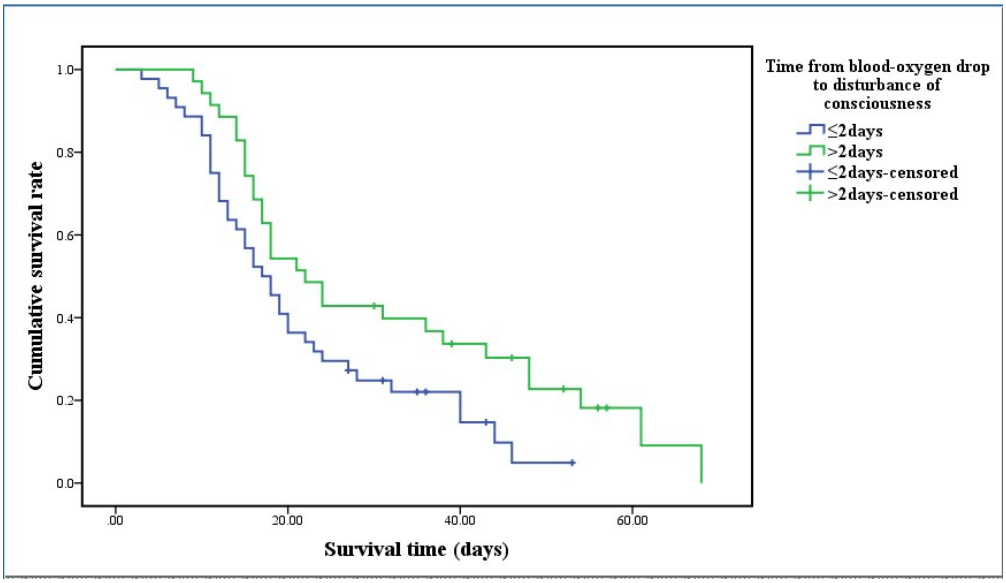

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Table 1. The risk factors of death in a multivariable Cox regression model (N=799*)

Characteristics	Survived (N=745) n(%)	Died (N=54) n(%)	HR	95%CI	P
Age(year)					
<65	593 (97.9)	13 (2.1)	1	-	-
≥65	152 (78.8)	41 (21.2)	1.82	(0.790, 4.194)	0.160
Gender					
Male	367 (92.2)	31 (7.8)	1	-	-
Female	378 (94.3)	23 (5.7)	1.058	(0.539, 2.076)	0.869
Current smoker					
No	618 (92.2)	52 (7.8)	1	-	-
Yes	127 (98.4)	2 (1.6)	0.727	(0.158, 3.348)	0.683
Acute complications					
No	419 (99.3)	3 (0.7)	1	-	-
Yes	326 (86.5)	51 (13.5)	1.238	(0.285, 5.367)	0.776
Comorbidities					
No	384 (96.0)	16 (4.0)	1	-	-
Yes	361 (90.5)	38 (9.5)	1.683	(0.790, 3.588)	0.178
Severity of COVID-19					
Mild	41 (95.3)	2 (4.7)	1	-	-

Moderate	511 (99.8)	1 (0.2)	0.17	(0.011, 2.565)	0.201
Severe	168 (93.9)	11 (6.1)	0.83	(0.156, 4.402)	0.827
Critical	25 (38.5)	40 (61.5)	0.765	(0.150, 3.896)	0.747
Blood oxygen level					
≥95%	541 (98.0)	11 (2.0)	1	-	-
90-94%	159 (97.5)	4 (2.5)	0.657	(0.192, 2.246)	0.503
85-89%	22 (75.9)	7 (24.1)	0.787	(0.268, 2.309)	0.663
<85%	23 (41.8)	32 (58.2)	2.093	(0.922, 4.749)	0.077
PH					
Normal	593 (96.1)	24 (3.9)	1	-	-
Deviation from normal <0.05	101 (93.5)	7 (6.5)	0.819	(0.325, 2.063)	0.672
Deviation from normal ≥0.05	51 (68.9)	23 (31.1)	0.88	(0.433, 1.791)	0.725
GCS					
15	737 (99.5)	4 (0.5)	1	-	-
14≥GCS ≥9	7 (30.4)	16 (69.6)	46.757	(10.346, 211.299)	<0.001
<9	1 (2.9)	34 (97.1)	65.855	(14.109, 307.385)	<0.001

*A further 65 individuals with missing value in survival time were excluded in the analysis.
GCS: Glasgow Coma Scale

Table 2. Difference in median survival time in different time groups

	Time span		Median survival time (days)	95% CI of median survival time (days)	HR *	95%CI of HR	P
Days from symptoms onset to disturbance of consciousness	<10 days	N=13; 12 died	11	(7.6, 14.4)	10.685	(4.4, 26.0)	<0.001
	10-19 days	N=46; 39 died	16	(14.1, 17.9)	4.106	(2.2, 7.7)	<0.001
	≥20 days	N=25; 19 died	40	(33.9, 46.1)	1	-	-
Days from deterioration of blood oxygen level to disturbance of consciousness	≤2 days	N=44; 38 died	17	(13.3, 20.7)	1.825	(1.1, 3.1)	0.026
	>2 days	N=35; 29 died	22	(16.2, 27.8)	1	-	-

CI: confidence interval; HR: hazard ratio

* Age, gender, and the severity of COVID-19 were adjusted