Upper Respiratory Tract Viral RNA Load at Hospital Admission is Associated with COVID-19 Disease Severity

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Abstract

Background

The outbreak of coronavirus disease 2019 (COVID-19) has aroused global public health concerns. Multiple clinical features relating to host profile but not for virus have been identified as the risk factors for illness severity and/or the outcomes in COVID-19.

Methods

The clinical features obtained from a cohort of 195 laboratory-confirmed, nasopharynx sampled patients with COVID-19 in Guangdong, China from Jan 13 to Feb 29, 2020 were subjected to this study. The differences in clinical features among four groups (mild, moderate, severe and critical) and between two groups (severe vs non-severe) were compared using one-way ANOVA and student's t-test, respectively. Principal component analysis and correlation analysis were performed to identify the major factors account for illness severity.

Results

Except the previously described clinical illness severity-related factors, including elder age, underlying diseases, higher level of CRP, D-dimer and AST, longer fever days and higher maximum body temperature, larger number of WBC and neutrophils but relative less lymphocytes, and higher ratio of neutrophil to lymphocytes, we firstly found that the initial viral load is an independent factor account for illness severity in COVID-19 patients.

Conclusions

The initial viral load of SARS-Cov-2 is a novel virological predictor for illness severity of COVID-19.

Keywords: viral load; COVID-19; SARS-CoV-2

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Introduction

The ongoing outbreak of coronavirus disease, 2019 (COVID-19), caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection,[1] has aroused global public health concerns and has been officially characterized as a pandemic by the World Health Organization (WHO) on Mar 11, 2020. Globally, there were more than 1,000,000 confirmed cases with over 50,000 deaths by 4 Apr, 2020 (https://www.who.int/), and the number of cases and deaths is still growing. The epidemiological surveys have indicated that most of patients only have mild symptoms, while there are not a few cases with severe symptoms[2-5] In contrast to the mild patients having good prognosis, the severe patients are more likely to have organ failure even death.[6] Given the lacks of therapeutics of proven effectiveness against SARS-Cov-2 infection, it's especially important to making appropriate management approach for the disease according to the severity of symptoms. It's thought that the identification of risk factors or predictors account for illness severity may provide valuable insight into the control of disease progress.

Several clinical parameters, including high Sequential Organ Failure Assessment (SOFA) score, elder age, low level of lymphocytes and pro-inflammatory cytokines, have been reported as the risk factors for illness severity or poor outcomes in recent retrospective studies.[7,8] Interestingly, all these reported factors are related to patients (namely the host); however, the virological risk features such as viral load have not yet been discovered. As a viral infectious disease that the interplay between the virus and the host defense determines the pathogenesis and clinical progress of the illness,[9] we speculated that, apart from the clinical parameters from host, the virological profile like initial viral load may also contribute to the severity of symptoms. Here we investigated the correlation between SARS-CoV-2 viral loads at hospital admission (in short initial viral load) and illness severity in a cohort of 195 patients in Guangdong, China.

Methods

Patients

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A cohort of 195 nasopharynx sampled laboratory-confirmed COVID-19 patients who were hospitalized at Guangzhou Eighth People's Hospital, the third affiliated hospital of Sun Yat-sen University, Yuedong Hospital and the first people's hospital of Foshan in Guangdong Province, China from January 13, 2020 to February 2020 were enrolled in this study. All patients did not receive any therapies before hospitalization, in addition to antipyretics. The diagnosis of COVID-19 and clinical classification were performed according to the New Coronavirus Pneumonia Diagnosis and Treatment Plan (trial version 3) released by the National Health Committee of the People's Republic of China (China NHC; http://www.nhc.gov.cn/). The study was approved by The Third Affiliated Hospital of Sun Yat-Sen University Yuedong Hospital Ethics Committee and written informed consent was obtained from patients involved before enrolment when data were collected retrospectively.

Baseline data collection

All suspected SARS-CoV-2 infection patients were taken nasopharynx swab sampling at admission and stored in virus transport medium, which were transported to Guangdong CDC for laboratory diagnosis. Epidemiological history, comorbidity, vital signs, symptoms and signs were recorded in detail, and laboratory tests including biochemical Indicators, blood routine, C-reactive protein, chest radiograph or CT scan.

Laboratory confirmation by real-time RT-PCR

The nasopharyngeal specimens from suspected patients were collected at admission, and were transported to Guangdong CDC for laboratory diagnosis. The RNA was extracted and tested by real-time RT-PCR with SARS-CoV-2 specific primers and probes targeting the N and Orf1b genes in accordance with the diagnosis protocol for COVID-19 established by WHO. The negative or positive for SARS-Cov-2 of samples is determined by the Cycle threshold (Ct) values of real-time RT-PCR: samples were considered as negative if Ct value exceeded 40 cycles, or positive if Ct value less than or equal to (≤) 40. The viral RNA copy number, converted from Ct value, is based on a standard curve of copy number versus Ct values of viral plasmid DNA. Each dilution of plasmid DNA was tested in duplicate to produce the standard curve.

Statistical analysis

According to the classification criterion (see detailed classification criteria in supplementary Method) of illness severity established by China NHC, all the confirmed COVID-19 patients were classified as mild, moderate, severe

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and critical groups. For dichotomous comparison, the mild and moderate groups were combined as non-severe groups, while the remaining severe and critical groups were combined as severe group.

Continuous data were presented with mean ± standard deviation (SD); while categorical data were presented with number and percentage (%). The statistical difference in continuous data between two groups (severe vs non-severe) were compared using Student's t-test; while the comparison in continuous among four groups (mild, moderate, severe and critical) were performed with one-way ANOVA, following a Tukey's post-hoc tests. Categorical data were tested using Chi-square test or Fisher's exact text (if expected value ≤ 5). Principal component analysis (PCA) was performed to identify the major contributing factors for illness severity. Where the rotation method for PCA plot was varimax with Kaiser normalization and the minimal component's initial eigenvalue was set at 1. P value < 0.05 was considered statistically significant for each two-tailed test. All analyses were performed using IBM SPSS Version 25 (SPSS Statistics V25, IBM Corporation, Somers, New York).

Results

Comparison of clinical and virological characteristics in 195 nasopharynx sampled patients

The clinical and virological characteristics of 195 nasopharynx sampled patients (94 males and 101 females), comprising 6 mild, 132 moderate, 41 severe and 6 critical patients, were summarized in Table 1. Their average age was 49.24±15.99 years old. The average time from onset to hospitalization, to be diagnosed, to be sampled and to turning negative were 3.65±3.24 days, 4.88±3.96 days, 6.69±4.66 days and 15.17±6.06 days, respectively. More severe patients seem to have elder age, higher frequency with underlying diseases, higher maximum body temperature within 24 hours after hospitalization, longer time for virus clearance (from illness onset to turning negative), duration of fever (days), higher plasma CRP, D-dimer, PCT and AST, larger count of white blood cells (WBC) and neutrophil (NE) but relative less lymphocyte (marginally significant; P = 0.095), higher neutrophil to lymphocyte ratio (NLR) and higher initial viral load [Ct and $\log_{10}$(copies/mL)] (except lymphocyte (P = 0.095) all P < 0.05; Table 1). Figure 1 further shows a significant increasing trend of initial viral load versus illness severity.

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To simplify the comparison, we classified these 195 nasopharynx sampled patients as two groups (non-severe: n=47 vs severe: n=148), namely combination of the mild and moderate groups as non-severe group while merging the critical patients into the severe group. As listed in supplementary Table S1, there were more elder patients in severe group; onset to hospitalization days, onset to turning negative days, fever rate, and highest body temperature in 24hr were bigger/longer/higher than non-severe group; significantly lower Ct and higher log_{10}(copies/mL) indicated higher viral load in severe group; higher level of CRP, WBC, NE, NLR, AST, D-Dimer, and PCT were observed in severe group (all $P<0.05$) (supplementary Table S1). A comparatively lower lymphocyte level in severe group was also observed (marginally significant $P=0.059$).

Predictive factors for illness severity

Principal component analysis (PCA) was performed to identification of major contributing factors for illness severity. To avoid bias estimation, only the variables whose missing rate lower than 30% would be used in this analysis. The overall KMO values was 0.582 and the explanatory ratio of variance reached 79.19% with 7 components comprising 1&5) the immune related features, 2) the time about illness onset to medical intervention, 3) age, 4) the indicator for liver failure (AST and ALT), 6) other (the turning negative time, basic diseases and sex), and 7) viral load as a single-variable component (supplementary Table S2).

Pearson's correlation coefficients between independent variables and severity or initial viral load were calculated to illustrate their relationships. As presented in Table 2, age, fever, peak body temperature in 24 hrs after hospitalization, CRP, WBC, NE, NLR, AST, D-Dimer and PCT are positively correlated with severity, no matter to be classified as four or two groups (all $P<0.05$). The time from illness onset to hospitalization (days) was only found to be positively correlated to dichotomous severity ($P<0.05$), while lymphocyte was only found to be significantly negative correlated to 4-grouped severity ($P<0.05$) (Table 2). As the two conversely correlated indexes for initial viral load, Log_{10}(copies/mL) and Ct value, were found to be respective significantly positive and negative correlated to severity (both in 4- and 2-grouped levels), we can conclude that the initial viral load is positive correlated to illness severity (Table 2).

Discussion

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In consistent with previous studies, our data also supports that several clinical features such as the patients age and the patients with/without underlying diseases are correlated to illness severity of COVID-19[4,10]. More importantly, we firstly identified the upper respiratory tract viral RNA load of SARS-Cov-2 at hospital admission as an independent predictive factor for illness severity. It suggests the patients with higher upper respiratory tract viral load at admission are more likely to develop severer symptoms and they may need more aggressive treatment.

It's thought that the interplay between virus and host immune response, rather than the single factor, determines the pathogenesis and disease progress of COVID-19[11-14]. The replication of SARS-Cov-2 do not directly lyse the host cells[15], but the virus-specific immune response may kill these cells[16]. It's possible that more virus (higher viral load) can infect more cells, and more alveolar cells, upon infected, may be killed by host immune system[17]. The acute, large quantity of cell death may contribute to the disease severity. Meanwhile, higher viral load may invoke stronger immune response, leading to release larger quantity of cytokines by the activated immune cells. There are evidences that a variety of pro-inflammatory cytokines such as IL2, IL6, IL7, IL10, IP10, IFNγ and TNFα at significant high level can promote disease severity[10].

Our study has some limitations, for example we just investigated the upper respiratory tract viral load while lacking the lower respiratory tract virological data. Secondly, because the detected samples may have mixed viral RNAs from dead virus, the viral RNA loads do not exactly equal to the titers or amounts of live infectious virus. Thirdly, there is difference, although it did not achieve statistical significance ($P > 0.05$), in the duration of viral RNA detection post hospitalization between different groups with varying degrees of symptoms. We noticed that the use of therapeutics (eg. antiviral drugs, convalescent palsma, corticosteroids and immunomodulators) may visibly affect viral loads; but this factor is ignorable in this study and it did little on initial viral load, because the patients did not receive drug treatment until they be diagnosed/sampled.

In summary, we identified that the upper respiratory tract viral RNA load of SARS-cov-2 at time of hospital admission is an independent prognostic factor of COVID-19.

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Conflict of interests

The authors declare no conflict of interest.

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Figure legends

Figure 1. The curve graph illustrating the differences in initial viral load among illness severity groups in 195 nasopharynx-sampled patients. The viral load was represented as (A) Ct value or (B) log_{10}(copies/mL). Y axis indicates the mean of Ct values (A) or logarithm value of viral RNA (B). The vertical lines on the curve represent standard deviation (SD).

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1 **Tables**

2 Table 1 Clinical and virological characteristics in 195 nasopharynx-sampled patients with COVID-19

Parameters	Mild (n=16)	Moderate (n=132)	Severe (n=41)	Critical (n=6)	All (n=195)	P
Sex						0.629
Male	6 (37.50%)	63 (47.73%)	21 (51.22%)	4 (66.67%)	94 (48.21%)	
Female	10 (62.50%)	69 (52.27%)	20 (48.78%)	2 (33.33%)	101 (51.79%)	
Age, year	36.63±16.25	47.32±15.32	58.39±12.49	62.67±15.06	49.24±15.99	<0.001
Age group						<0.001
<50	12 (75.00%)	73 (55.30%)	7 (17.07%)	1 (16.67%)	93 (47.69%)	
>=50	4 (25.00%)	59 (44.70%)	34 (82.93%)	5 (83.33%)	102 (52.31%)	
BMI	23.15±3.00	23.91±4.07	24.60±4.33	24.02±4.39	24.00±4.05	0.663
Basic diseases						
Hypertension	5 (33.33%)	16 (14.55%)	8 (32.00%)	0 (0.00%)	29 (19.21%)	0.109
Diabetes mellitus	2 (13.33%)	2 (1.82%)	1 (4.00%)	0 (0.00%)	5 (3.31%)	0.291
Cardiovascular disease	0 (0.00%)	7 (6.36%)	3 (12.00%)	0 (0.00%)	10 (6.62%)	0.367
Cerebrovascular disease	0 (0.00%)	2 (1.82%)	2 (8.00%)	0 (0.00%)	4 (2.65%)	0.390
Chronic kidney disease	0 (0.00%)	1 (0.91%)	2 (8.00%)	0 (0.00%)	3 (1.99%)	0.249
All above diseases	6 (40.00%)	22 (20.00%)	11 (44.00%)	0 (0.00%)	39 (25.83%)	0.047

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Onset to hospitalization (days)	4.19±4.42	3.24±2.79	4.39±3.51	6.00±5.44	3.65±3.24	0.048
Onset to diagnosed (days)	5.57±5.02	4.75±3.98	4.90±3.56	5.83±4.07	4.88±3.96	0.822
Onset to be sampled (days)	5.75±4.20	6.58±4.55	7.38±5.18	7.00±4.98	6.69±4.66	0.659
Onset to turning negative (days)	12.44±4.98	13.69±4.90	19.71±6.39	24.17±6.88	15.17±6.06	<0.001
Fever days	5.38±4.60	6.93±5.59	9.26±5.75	6.20±2.05	7.32±5.56	0.141
Maximum body temperature in 24hrs	37.80±0.89	37.80±0.78	38.53±0.74	38.02±0.54	38.00±0.82	0.002
Fever						0.014
No	7 (43.75%)	36 (27.27%)	5 (12.20%)	0 (0.00%)	48 (24.62%)	
Yes	9 (56.25%)	96 (72.73%)	36 (87.80%)	6 (100.00%)	147 (75.38%)	
Ct	33.74±3.92	33.59±4.45	32.10±4.64	27.53±2.63	33.10±4.54	0.004
Log_{10} (copies/mL)	3.36±0.93	3.40±1.06	3.75±1.10	4.84±0.62	3.51±1.08	0.004
CRP (mg/dL)	14.93±18.93	16.29±14.78	30.11±32.19	39.59±16.64	19.82±20.92	<0.001
WBC (10^9/L)	5.80±1.11	4.96±1.82	5.92±2.71	7.74±6.76	5.35±2.41	0.009
Neutrophil (10^9/L)	3.08±1.29	3.06±1.45	4.27±2.79	6.21±6.00	3.47±2.23	<0.001
Lymphocyte (10^9/L)	1.89±0.75	1.46±0.93	1.24±0.56	1.08±0.82	1.42±0.85	0.095
NLR	2.16±1.99	2.53±1.61	5.07±5.25	6.70±5.16	3.26±3.28	<0.001
AST (U/L)	22.51±10.48	23.89±15.79	30.90±17.60	48.48±28.52	26.35±17.20	0.001

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ALT (U/L)	25.93±10.84	28.80±24.48	34.55±20.71	35.87±16.82	30.21±22.75	0.469
D-Dimer (mg/L)	934.00±340.27	1495.14±3637.77	3358.85±6227.96	10230.00±0.00	1900.67±4258.42	0.046
PCT (μg/L)	17.92±26.72	41.28±61.11	141.88±271.22	1068.00±0.00	68.46±165.89	<0.001

BMI, body mass index; Ct, Cycle threshold value; CRP, C-reactive protein; NLR, Neutrophil/Lymphocyte Ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PCT, Procalcitonin

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Table 2 Pearson's correlation coefficients between variables and illness severity

	Severity (4 levels)	Severity (2 levels)
Ct	-0.22*	-0.20*
Log10 (copies/mL)	0.22*	0.20*
Onset to hospitalization	0.13	0.17*
Onset to be sampled	0.08	0.08
Onset to turning negative	0.46*	0.48*
Age	0.39*	0.34*
Age group (≥50 or not)	0.34*	0.35*
Sex	-0.09	-0.06
BMI	0.10	0.10
Fever	0.21*	0.18*
Fever days	0.14	0.16
Peak body temperature in 24hrs	0.28*	0.37*
CRP	0.30*	0.31*
WBC	0.19*	0.21*
NE	0.30*	0.29*
Lymphocyte	-0.19*	-0.15
NLR	0.37*	0.38*
AST	0.28*	0.25*
ALT	0.12	0.12
D-Dimer	0.22*	0.21*
PCT	0.40*	0.35*

BMI, body mass index; Ct, Cycle threshold value; CRP, C-reactive protein; NLR, Neutrophil to Lymphocyte Ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PCT, Procalcitonin. * indicates $P < 0.05$.

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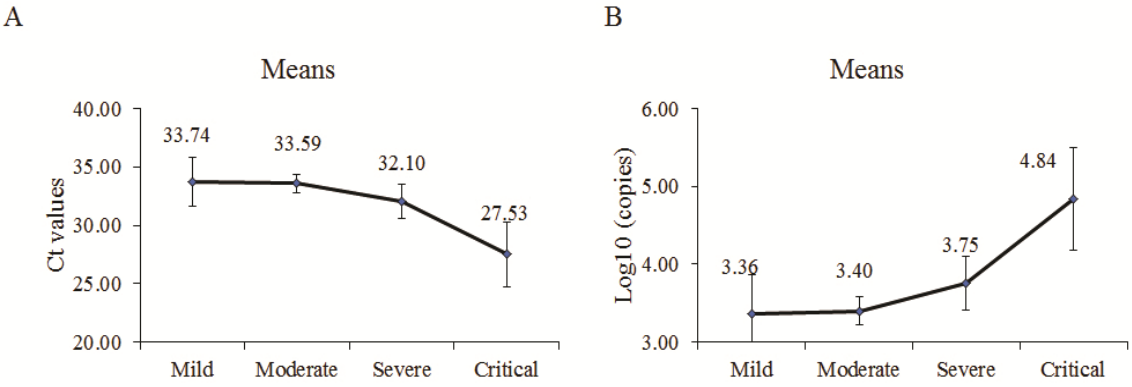
9 Figure 1



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