Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients

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Summary

Detectable serum SARS-CoV-2 viral load (RNAaemia) was confirmed only in the critically ill patient group and appeared to reflect the illness severity. Besides, the extremely high interleukins 6 (IL-6) level was closely correlated with the incidence of RNAaemia and the vital signs of coronavirus disease-19 (COVID-19) patients.

Running title: Relationship between RNAaemia and COVID-19 severity

Abstract

Background:

Although the detection of SARS-CoV-2 viral load in respiratory specimens has been widely used to diagnose coronavirus disease-19 (COVID-19), it is undeniable that serum SARS-CoV-2 nucleic acid (RNAaemia) could be detected in a fraction of COVID-19 patients. However, it is not clear whether testing for RNAaemia is correlated with the occurrence of cytokine storms or with the specific class of patients.

Methods:

This study enrolled 48 patients with COVID-19 admitted to the General Hospital of Central Theater Command, PLA, a designated hospital in Wuhan, China. The patients were divided into three groups according to the "Diagnosis and Treatment of New Coronavirus Pneumonia (6^{th} edition)" issued by the National Health Commission of China. The clinical and laboratory data were collected. The serum viral load and IL-6 levels were determined. .

Results:

Clinical characteristics analysis of 48 cases of COVID-19 showed that RNAaemia was diagnosed only in the critically ill group and seemed to reflect the severity of the disease. Furthermore, the level of inflammatory cytokine IL-6 in critically ill patients increased significantly, almost 10 times that in other patients. More importantly, the extremely high IL-6 level was closely correlated with the detection of RNAaemia (R = 0.902).

Conclusions:

Detectable serum SARS-Cov-2 RNA(RNAaemia) in COVID-19 patients was associated with elevated IL-6 concentration and poor prognosis. Because the elevated IL-6 may be part of a larger cytokine storm which could worsen outcome, IL-6 could be a potential therapeutic target for critically ill patients with an excessive inflammatory response.

Keywords

Coronavirus disease-19 (COVID-19); RNAaemia; IL-6; critically ill patients; pneumonia; cytokine storm

Introduction

The coronavirus disease-19 (COVID-19) caused by the SARS-CoV-2 virus infection has been described by the world health organization (WHO) as a public health emergency of international concern[1-3]. As of April 12, 2020, more than 1,600,000 cases of COVID-19 have been reported globally to the World Health Organization (WHO), with more than 99,000 deaths.

SARS-CoV-2 and SARS-CoV likely use the same angiotensin-converting enzyme 2 (ACE2) as the entry receptor[4-6], but the clinical manifestations of the two diseases are different. After infection, patients with COVID-19 may develop mild, moderate or severe symptoms. The mild patients maybe asymptomatic.Moderate patients may exhibit symptoms of fever, nonproductive cough, dyspnea, myalgia, fatigue, and radiographic evidence of pneumonia; most of them appear to have a good prognosis. In contrast, some patients may develop severe pneumonia, acute respiratory distress syndrome (ARDS) or multiple organ failure[7-10]. Importantly, in critically ill patients, SARS-CoV-2 infection is also associated with inflammatory cytokine storm[11, 12], which is mainly characterized by elevated plasma concentration of interleukins 6 (IL-6). Several recent COVID-19 clinical studies have shown that the level of IL-6 in the severe group was higher than that in the moderate group[11, 13-15], suggesting that IL-6 can be used as a biomarker for severity assessment. However, how to quantitatively correlate IL-6 levels with critically ill patients is still unknown.

Real-time reverse transcription-polymerase chain reaction assay (RT-PCR) with primers and probes targeting the nucleocapsid protein (N) and open reading frame 1ab (ORF1ab) genes of SARS-CoV-2 from throat swab samples has been widely used in the diagnosis of COVID-19 patients. A recent study showed that the viral load in respiratory specimens of symptomatic patients was similar to that of asymptomatic patients[16], implying that the viral load in respiratory specimens may not objectively reflect the disease severity. Serum SARS-CoV-2 viral RNA (termed as RNAaemia by the authors in a recent study) was detected in 15% of the COVID-19 patients[8], but the relevant characterizations are still lacking. In particular, it is unclear whether RNAaemia can be considered as a prognostic indicator, especially for severe or critically ill patients.

In this study, we systematically quantified the serum SARS-CoV-2 viral load (RNAaemia) of various patient groups and characterized the relationship between RNAaemia, IL-6 level, and disease severity.

Methods

Data collection

This retrospective study was approved by the Ethics Committee of General Hospital of Central Theater Command. Oral consent was obtained from patients. Pharyngeal swab samples collected at General Hospital of Central Theater Command from February 1 to February 19, 2020 confirmed 48 enrolled COVID-19 patients by real-time reverse transcription-polymerase chain reaction assay (RT-PCR). Immediately after admission, the patients' specimens for interleukins 6 (IL-6) and viral RNA levels were obtained. Their medical records were collected, including epidemiology, demographics, clinical manifestations, radiological characteristics, laboratory data, and outcome data. All data were checked by a team of trained physicians.

Laboratory examination

Serum samples and throat-swabs were collected from all patients and RNA was extracted. RT-PCR was used to determine the viral load by using a SARS-CoV-2 nucleic acid detection kit (DAAN GENE Ltd., Guangzhou, China, Cat# DA0930-DA0932). Two target genes were amplified and tested simultaneously, namely the open reading frame 1ab (ORF1ab) and nucleocapsid protein (N). According to the manufacturer's procedures, a cycle threshold value (Ct-value) of less than 40 was defined as a positive result, and a Ct-value of 40 or more was defined as a negative result. Specimens, including sputum or alveolar lavatory fluid, blood, urine, and feces, were cultured to identify pathogenic bacteria or fungi that may be associated with the SARS-CoV-2 infection. The level of inflammatory cytokine IL-6 was measured using a kit from Roche Ltd (Mannheim, Germany, Cat# 05109442190).

Statistical Analysis

According to the "Diagnosis and Treatment of New Coronavirus Pneumonia (6th edition)" issued by the National Health Commission of China, COVID-19 patients were classified. There was no mild case in the enrolled patients. Classification variables were described as frequency ratios or percentages, and the significance was detected by the chi-square test or Fisher's exact test. The quantitative variables of parameters were

expressed as the mean ± standard deviation, and the significance was tested by the t-test. For items that did not conform to the normal distribution, the significance was determined by the Kruskal Wallis test. SPSS statistical software (Macintosh version 26.0, IBM, Armonk, NY, USA) and R program were used for statistical analysis.

For testing the differences of the negative and positive qPCR patients, multi-response permutation procedure was used with Bray-Curtis method. The null hypothesis was that there was no difference among the groups in a Monte Carlo randomization procedure with 999 permutations. The P value < 0.05 was considered statistically significant.

Results

Characteristics of COVID-19 patients enrolled in this study

A total of 48 laboratory-confirmed patients were enrolled in the study. According to the Guidelines of the "Diagnosis and Treatment of New Coronavirus Pneumonia (6th edition)" issued by the National Health Commission of China, the COVID-19 patients were categorized into three groups: 21 moderate cases (43.7%), 10 severe cases (20.8%), and 17 critically ill cases (35.4%). Severe patients also met at least one of the following conditions: (1) shortness of breath with the respiratory rate (RR) ≥ 30 times/min, (2) oxygen saturation at resting state ≤ 93%, or (3) PaO2/FiO2 ≤ 300 mmHg. The admission of critically ill patients must meet at least one of the following additional conditions: (1) respiratory failure requiring mechanical ventilation; (2) shock, and (3) multiple organ failure requiring transfer to the intensive care unit (ICU). Three patients in the critical group died after disease onset.

As shown in **Table 1**, the enrolled COVID-19 patients consisted of 31 males (77.1%) and 17 females (22.9%). The critically ill patients (79.6 ± 12.6 years) were older than the severe patients (63.9 ± 15.2 years) and the moderate patients (45.8 ± 14.2 years) without statistical significance, and the majority of severely ill patients were male (88.2%), displaying an age- and male-dependent severity. Notably, several underlying diseases were implicated in the COVID-19 patients, among which high-risk factors included diabetes (12 [25%]), hypertension (23 [49.7%]), and heart disease (8 [16.7%]). Mixed fungal infection was found in 27.1% of patients, and bacteria did not seem to be common (2.1%).

Serum SARS-CoV-2 nucleic acid is only detectable in critically ill patients

We examined the SARS-CoV-2 viral load in patient serum using real-time RT-PCR. As shown in **Figure 1A and B**, 5 out of 48 cases (10.4%) were confirmed as positive (the number of patients tested positive for the N gene was 3 and for the ORF1ab gene was 5), which was similar to a previous study[8]. Interestingly, although all patients' pharyngeal swab samples were tested positive, serum samples from the moderate or severe group did not show a positive result. In contrast, all five positive results were from critically ill patients, two of whom died after the onset of COVID-19 (**Table S1**). Respiratory failure was the leading cause of all deaths. The underlying diseases were found in one death with positive RNA (hypertension) and one death without positive RNA (hypertension and diabetes). Other RNA-positive patients had no comorbidities.

Since inflammatory cytokine storms frequently occur in critically ill COVID-19 patients, we then investigated whether any laboratory parameters are associated with RNAaemia and have an impact on the severity of COVID-19.

Sharply increased IL-6 level is strongly associated with the COVID-19 severity

As shown in **Table 2**, the absolute count of peripheral blood lymphocytes was lower in severe patients than in moderate patients, and even lower in critical patients, which was consistent with recent reports[17, 18]. Whereas the absolute count of neutrophils was higher in critically ill patients. The procalcitonin (PCT) level in critically ill patients was higher than that in the other two groups and similar to other clinical observation[19], indicating a significantly increased inflammatory response in these patients. Remarkably, sharply increased IL-6 level was observed in critically ill patients, which was almost 10 times that of severe patients, and all deaths exhibited extremely high IL-6 value (**Table S1**), suggesting that IL-6 might be an important biomarker to judge the poor prognosis of COVID-19 patients. The extremely high level of IL-6 is a hallmark and important driving force of cytokine storm[20], which may cause multiple organ dysfunction in critically ill patients[12]. Consistently, the parameters that reflect organ dysfunction, including TnT (troponin T), CRE (serum creatinine), and BUN (blood urea nitrogen), were higher in critically ill patients compared with the other two groups.

RNAaemia is closely associated with IL-6 level in critically ill COVID-19 patients

In a recent study, RNAaemia has been linked to COVID-19[8]. Our data strongly

suggest that both RNAaemia and IL-6 concentration ⩾ 100 pg/mL were exclusively observed in critically ill patients, which prompted us to further study the relationship between them. As shown in **Figure 2A**, patients with RNAaemia exhibited a much higher IL-6 level compared with other patients. We then checked the IL-6 value in each RNAaemia patient. Strikingly, all of their IL-6 values exceeded 100 pg/mL (**Table S1**). To further confirm the relationship between them, we first analyzed the IL-6 values of critically ill patients. Notably, mortality appeared to be associated with an IL-6 value of ⩾100 pg/mL, since all deaths in this study were in this group (**Table S1**). We, therefore, defined the IL-6 value of ⩾100 pg/mL as high and the rest as low. In the critically ill group, patients with high IL-6 accounted for 35.3% (**Figure 2B**). As shown in **Table 3**, the incidence of RNAaemia was closely correlated with high IL-6 level in critically ill patients (R = 0.902). These data demonstrated that RNAaemia was related to a poor prognosis. Indeed, compared with patients without RNAaemia, all patients with RNAaemia had a higher risk of multiple organ damage (**Figure 3A-C**).

Discussion

Although the detection of throat swab rather than serum SARS-CoV-2 viral load is widely used for COVID-19 diagnosis, an undeniable fact is that serum SARS-CoV-2 nucleic acid (RNAaemia) is only detectable in some patients[8]. However, it is not clear under what circumstances it can be detected and whether the incidence of RNAaemia is related to certain types of patients. In this study, we investigated the distribution of RNAaemia-positive cases in each patient group and found that these cases were only confirmed in critically ill patients, which indicates that RNAaemia is not a casual event. Moreover, the laboratory data analysis strongly suggests that the level of inflammatory cytokine IL-6 in critically ill patients was significantly elevated. More importantly, the extremely high IL-6 level was closely correlated with the incidence of RNAaemia and mortality. Based on our observations and literature reports, older males with underlying diseases, high IL-6 levels, and detectable RNAaemia are more likely to have adverse clinical outcomes. Our work may provide clues for developing new COVID-19 diagnostic strategies and therapeutic targets.

Although recent studies have shown that IL-6 level increased in severe patients[14], its level in critically ill COVID-19 patients is still unknown. IL-6 is one of the main pro-inflammatory factors that contribute to the formation of cytokine storms, which largely enhance the vascular permeability and impair the organ function. This

observation might help explain why RNAaemia can be detected only in patients with an extremely high level of IL-6. We still cannot rule out the possibility that the SARS-CoV-2 virus population explodes in a short period, which in turn triggers a cytokine storm characterized by increased levels of cytokines such as IL-6. Therefore, the combination of the IL-6 level and serum viral RNA Ct-value may be regarded as an effective marker for standard clinical measures to predict impending adverse outcomes with high accuracy. We must point out that due to the shortage of detection kits, results of other cytokines cannot be obtained and those investigations should be warranted in future studies.

Host-oriented therapies should be selected because of the high mortality rate in critically ill patients with COVID-19. IL-6 functions as a critical mediator of respiratory failure, shock, and multi-organ dysfunction[21]. Whether IL-6 can be a therapeutic target for critically ill patients is a direction worth studying. Notably, the IL-6R monoclonal antibody (Tocilizumab)-directed COVID-19 therapy has been used in the clinical trial in China (No.ChiCTR2000029765). And it has recently been incorporated into COVID-19 management guidelines generated in China and Italy. Our data strongly supported this notion, but the efficacy of IL-6 monoclonal antibody-directed therapy remains to be fully evaluated. Besides, our observations also indicate that the combination of antiviral and anti-inflammatory treatments may be important for critically ill COVID-19 patients. Therefore, Baricitinib, a powerful inhibitor of the IL6/JAK/STAT signaling pathway and the clathrin-mediated endocytosis, may be effective against the consequences of elevated cytokine levels and SARS-CoV-2 infection in severe COVID-19 patients[22, 23].

NOTES

Contributors

FL and JD conceived and designed the study. FL, XC, YF, and DM contributed to the literature search. XC, BZ, QH, YL, BY and JD contributed to data collection. XC, YQ, YC, and FL contributed to data analysis. FL and XC contributed to data interpretation. YQ and XC contributed to the figures. FL, XC, and JX contributed to the writing of the report.

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Declaration of interest

We declare no competing interests.

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Figure Legends

Figure 1: **Serum SARS-Cov-2 nucleic acid was exclusively detected in critically ill patients**. The histogram indicates the ratio of cases with positive values of (**A**) nucleocapsid protein (N) or (**B**) open reading frame 1ab (ORF1ab) in each patient group.

Figure 2: (**A**) The average IL-6 value in cases with (P) or without (N) RNAaemia; (**B**) The ratio of patients with the high expression level of IL-6 (≥ 100 pg/mL) in each group.

Figure 3: The average values of TnT, CRE, and BUN in cases with (P) or without (N) RNAaemia. TnT, troponin T; CRE, serum creatinine; BUN, blood urea nitrogen. Moderate, moderate patients.

Table 1. Demographics and baseline characteristics of patients infected with SARS-CoV-2.

Baseline variables	All patients (N=48)	Moderate patients (N=21)	Severe patients (N=10)	Critically ill patients (N=17)	*p*-value
Characteristics					
Age(year)	64.6±18.1	52.8±14.2	63.9±15.2	79.6±12.6	0.124
Gender (%)					< 0.001
Men	37 (77.1)	13 (61.9)	9 (90)	15 (88.2)	
Women	11 (22.9)	8 (38.1)	1 (10)	2 (11.8)	
Huanan seafood market exposure (%)	1 (2.1)	0 (0)	0 (0)	1 (5.9)	0.002
Underlying diseases (%)					
Diabetes	12 (25)	4 (19.0)	1 (10)	7 (41.2)	<0.05
Hypertension	23 (49.7)	6 (28.6)	5 (50)	12 (70.6)	< 0.001
Pulmonary disease	2 (4.2)	1 (4.8)	0 (0)	1 (5.9)	0.043
Hepatic disease	4 (8.3)	3 (14.3)	0 (0)	1 (5.9)	< 0.001
Heart disease	8 (16.7)	2 (9.5)	1 (10)	5 (29.0)	< 0.001
Cerebral disease	6 (12.5)	2 (9.5)	0 (0)	4 (23.5)	< 0.001
Thyroid disease	4 (8.3)	2 (9.5)	0 (0)	2 (11.8)	< 0.001
Malignancy	6 (12.5)	1 (4.8)	2 (20)	3 (17.6)	0.005
Co-infection (%)					0.006
Fungi	13 (27.1)	1 (4.8)	6 (60)	6 (35.3)	< 0.001
Bacteria	1 (2.1)	0 (0)	0 (0)	1 (5.9)	0.004

Table 2. Comparison of laboratory parameters in moderate, severe and critically ill COVID-19 patients.

Baseline variables	All patients (N=48)	Moderate patients (N=21)	Severe patients (N=10)	Critically ill patients (N=17)	*p*-value
White blood cell ($\times 10^9$/L)	5.75 (4.13-8)	5.2 (4.6-6.1)	4.1 (3.3-5.78)	8.4 (6.1-10.6)	＜0.05
Neutrophil ($\times 10^9$/L)	3.8 (2.7-6.6)	3.4 (2.8-4.3)	2.9 (2.0-3.78)	7.1 (5.3-9.2)	＜0.05
Lymphocyte ($\times 10^9$/L)	0.95±0.54	1.25±0.46	0.90±0.30	0.59±0.55	＜0.05
IL-6 (pg/ml)	18.1 (4.5-49)	10.4 (3.8-31.0)	5.8 (3.1-16.9)	64.0 (25.6-111.9)	＜ 0.001
PCT (ng/ml)	0.06 (0.04-0.13)	0.04 (0.03-0.06)	0.04 (0.04-0.06)	0.20 (0.1-0.6)	＜0.05
TnT (ng/ml)	0.01 (0.008-0.03)	0.008 (0.005-0.01)	0.009 (0.007-0.01)	0.03 (0.02-0.06)	＜ 0.001
CRE (μmol/L)	64.5 (55.0-77.0)	63.0 (50.0-71.0)	56.0 (52.0-73.8)	77.0 (64.0-101.0)	＜0.05
BUN (mmol/L)	5.6 (3.8-7.9)	4.0 (3.5-5.1)	4.2 (2.6-7.8)	9.3 (7.5-13.7)	＜0.05

Abbreviations: IL-6, interleukin-6; PCT, procalcitonin; TnT, troponin T; CRE, serum creatinine; BNU, blood urea nitrogen.

Table 3. The correlation analysis of RNAaemia incidence or vital signs and serum IL-6 level in 48 COVID-19 patients.

Baseline variables	All patients (N=48)	IL-6 (＜100 pg/ml) (N=42)	IL-6 (＞100 pg/ml) (N=6)	R	*p*-value
RNAaemia				0.902	＜0.001
Negative (%)	43	42（100）	1（16.7）		
positive (%)	5	0（0）	5（83.3）		
Vital signs				-0.683	0.001
death (%)	3	0 (0)	3 (50)		
alive (%)	45	42 (100)	3 (50)		

Figure 1

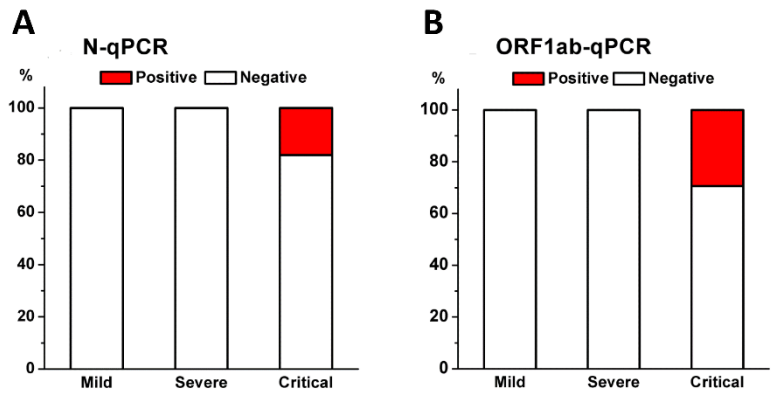

Figure 2

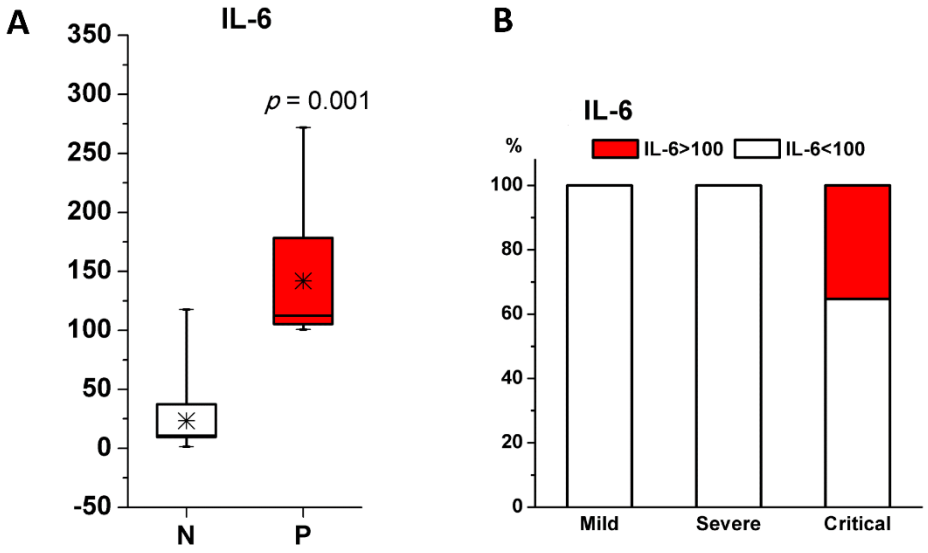

Figure 3