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Dynamics of Blood Viral Load Is Strongly Associated with Clinical Outcomes in Coronavirus Disease 2019 (COVID-19) Patients

A Prospective Cohort Study

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The prevalence and clinical relevance of viremia in patients with coronavirus disease 2019 (COVID-19) have not been well studied. A prospective cohort study was designed to investigate blood viral load and clearance kinetics in 52 patients (median age, 62 years; 31 [59.6%] male) and explore their association with clinical features and outcomes based on a novel one-step RT droplet digital PCR (RT-ddPCR). By using one-step RT-ddPCR, 92.3% (48 of 52) of this cohort was quantitatively detected with viremia. The concordance between the blood and oropharyngeal swab tests was 60.92% (53 of 87). One-step RT-ddPCR was tested with a 3.03% false-positive rate and lower 50% confidence interval of detection at 54.026 copies/mL plasma. There was no reduction in the blood viral load in all critical patients, whereas the general and severe patients exhibited a similar ability to clear the viral load. The viral loads in critical patients were significantly higher than those in their general and severe counterparts. Among the 52 study patients, 30 (58%) were discharged from the hospital. Among half of the 30 discharged patients, blood viral load remained positive, of which 76.9% (10 of 13) completely cleared their blood viral load at follow-up. Meanwhile, none of their close contacts had evidence of infection. Quantitative determination of the blood viral test is of great clinical significance in the management of patients with coronavirus disease 2019. *(J Mol Diagn 2021, 23: 10–18; https://doi.org/10.1016/j.jmoldx.2020.10.007)*

The end of 2019 witnessed an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated coronavirus disease 2019 (COVID-19) in Wuhan, China.[1] By April 3, 2020, more than 1,000,000 cases and >50,000 deaths were confirmed worldwide. The rapid global spread of COVID-19 has led to subsequent declaration of a pandemic by the World Health Organization.[2] Currently, a great number of clinical challenges concerning COVID-19 need to be addressed urgently. Mounting evidence shows that the SARS-CoV-2 test of respiratory specimens turns positive for the virus after discharge,[3] which raises concerns about the possible transmission via these patients.

To improve SARS-CoV-2 testing sensitivity, researchers have tried different sampling locations. Peripheral blood should theoretically be an ideal sampling

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all critical patients failed to eliminate blood viral load. In contrast, the general and severe patients were equally capable of completely clearing the blood viral load. Second, blood viral load was found to be associated with the severity of COVID-19. The viral load was significantly higher in critical patients than in their general/severe counterparts, which could be, at least partially, ascribed to the impaired capability to generate SARS-CoV-2–specific antibodies on the part of critical patients. Among the patients whose condition deteriorated, a corresponding rise in blood viral load was detected. Interestingly, although there was no significant difference in the level of blood viral load between the general and severe patients, the severe patients exhibited a stronger inflammatory response, as defined by high-sensitivity C-reactive protein level. This finding provides a rationale for a prospective clinical trial to reduce the overactivated host inflammatory response in severe patients. Moreover, no significant difference was found in the levels of cytokines between the general and severe patients, suggesting that other cytokines or chemokines might be more crucial for the immunopathologic changes.

Finally, 30 patients met the current discharge criteria, and blood viral load remained positive in 15 of these patients. Consistent with our data, other independent studies have reported frequent detection of nucleic acid of SARS-CoV-2 in urine and stool.[12] These findings raise serious concerns over the long-term outcome and infectivity of these patients, which present future public health issues. Ten of the 13 discharged patients completely cleared their blood viral load, as indicated by our follow-up (spanning 45 to 61 days from the illness onset to the follow-up). Moreover, none of their close contacts exhibited evidence of infection, as indicated by ddPCR. Our results suggest that the clearance of blood SARS-CoV-2 might take longer than expected and occurs in a gradual manner. Nevertheless, there was no evidence suggesting that the patients in the course of viral clearance were contagious. The most recent publication from the Wendtner group has confirmed our findings.[13] Although further investigation in a large cohort is warranted to draw definitive conclusions, the current findings are very encouraging.

This study has important clinical implications. By using this method, were able to detect viremia in 92.3% of our cohort, which can serve as a useful tool for diagnosis, monitoring therapeutic response in terms of viral load, confirming the viral clearance, and following up with patients after discharge. Our study further supports the notion that COVID-19 is a self-limited disease, with most of the general and severe cases capable of completely clearing their viral load. Conversely, critical patients seem to be a distinct subgroup, characterized by defective viral clearance,[14] lower levels of SARS-CoV-2–specific antibodies, and a strong inflammatory response. The management of COVID-19 should therefore be tailored because of the heterogeneous nature of these patients. For the general/severe cases, supportive therapies could be essential, and, with some severe cases, immunomodulatory therapies might be explored to suppress aberrant host inflammatory response. For the critical patients, antiviral therapy, in combination with anti-inflammatory and supportive treatments, should be considered and tested in a clinical trial setting to improve clinical outcomes. In this regard, dynamic monitoring of blood viral load by RT-ddPCR will assist physicians in identifying and monitoring the early signs of aggravation in critical cases. Finally, our study showed that the viremia in patient DF and other critical patients did not suffice to produce SARS-CoV-2–specific antibodies, suggesting that the host humoral immunity plays a critical part in the removal of SARS-CoV-2, and the vaccines and therapeutic antibodies promise to be effective for the prevention and cure of COVID-19.

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Author Contributions

W.W., J.Zho. concieved and designed the study; L.C., G.W., X.L., H.H., J.T., J.W., Y.C., W.L. acquired and analyzed data; J.Zha., Y.C., Lia.H., F.M., Lif.H., N.W. provided care to patients and provided clinical information; J.Zho., J.W., L.C., G.W., Y.C. wrote the manuscript; J.Zho., W.W., Z.S., G.H., J.Zha. revised the manuscript; L.C., X.L., Y.C. performed statistical analysis; W.W., J.Zho. obtained funding; W.W., J.Zho. supervised the study.

Supplemental Data

Supplemental material for this article can be found at *http://doi.org/10.1016/j.jmoldx.2020.10.007*.

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