

# Peripheral Lymphocyte Count and Viral Clearance in COVID-19

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## ABSTRACT

The objective of the study was to investigate whether the peripheral lymphocyte count was independently negative association with viral clearance time of SARS-CoV-2 in Chinese patients with COVID-19. Total 202 patients were chosen for the last data analysis. The patients' mean age was  $41.39 \pm 12.47$  years. Male was accounted for 48.51% and female was 51.49% respectively. The average viral clearance time was  $19.40 \pm 9.03$  days. Adjusted linear regression result showed peripheral lymphocyte count was associated with viral clearance time negatively after adjusting confounders ( $\beta$ , -2.79; 95% CI, -5.21 to -0.36). The trend of peripheral lymphocyte count treated as a categorical variable in linear regression was also consistent with the result when peripheral lymphocyte count was treated as a continuous variable. There was a negative association between peripheral lymphocyte count and viral clearance time of SARS-CoV-2 in Chinese patients with COVID-19.

**Key Words:** Peripheral lymphocyte count, Viral clearance, COVID-19.

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Coronavirus Disease 2019 (COVID-19) is a significant global health-emergency resulted from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The viral clearance time of SARS-CoV-2 is an important element for the treatment and prevention of COVID-19. The turning negative of SARS-CoV-2 RNA is one of the significant criteria for discharge.<sup>1</sup> Peripheral lymphocyte count is a simple inflammation biomarker and is easily obtained. Lymphocyte is also the chief immune cell that battle with SARS-CoV-2.<sup>2</sup> It has been observed that the peripheral lymphocyte count was closely related to the severity and prognosis of COVID-19.<sup>3</sup>

However, viral clearance time in adults with COVID-19 has not been well explored. Findings from prior studies concerning the relationship between the peripheral lymphocyte count and viral clearance time of SARS-CoV-2 were limited and inconsistent.<sup>4-6</sup> Therefore, this research gathered the laboratory test results of patients at the time of admission and aimed to evaluate the relationship between the peripheral lymphocyte count and virus clearance time of SARS-CoV-2.

The study was approved by the Research Ethics Commission of the First Affiliated Hospital of Xiamen University, China (M2021069). The study gathered a sum of 227 patients initially. The entry time and deadline for inclusion were September 12 to October 03, 2021, respectively. The entire clinical practice for every patient was conducted according to Chinese recommendations for the diagnosis and treatment of novel coronavirus (SARS-CoV-2) infection (Trial 8th version).<sup>1</sup> Inclusion criteria were patient hospitalisation with confirmed COVID-19 by a positive result of RT-PCR analysis for SARS-CoV-2 in nasopharyngeal swabs. Exclusion criteria were age less than 14 years. After exclusion, 202 subjects remained for the final analysis.

According to published guidelines and research, the authors obtained the demographic, clinical, laboratory, therapy, and outcome data from the hospital information system. The demographic, clinical and laboratory data were gathered at the baseline (the time of admission). Disease severity definition: Mild was defined as mild symptoms without radiology-confirmed pneumonia; general was defined as fever or respiratory system symptoms with radiology-confirmed pneumonia; severe was defined as respiratory rate  $\geq 30$  per minute or peripheral oxygen saturation rate  $\leq 93\%$  or arterial oxygen pressure ( $\text{PaO}_2$ )/fraction of inspiration oxygen ( $\text{FiO}_2$ )  $\leq 300\text{mmHg}$  ( $1\text{mmHg} = 0.133\text{kPa}$ ) adjusted by altitude or radiology-confirmed pulmonary lesions progressing by more than 50% within 24-48 hours; critically severe was defined as respiratory failure requiring mechanical ventilation or shock or multiple organ failure requiring close monitoring in the intensive care unit.<sup>1</sup> That the peripheral lymphocyte count less than  $0.8 \times 10^9/\text{L}$  is defined as lymphocytopenia. Nasopharyngeal swab samples were taken

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for analysis at baseline and then tested every 2-3 days until discharge or two weeks later. Then samples were taken for analysis every day after two weeks if not discharged. SARS-CoV-2 RNA was detected using the TaqMan probe targeting ORF1ab, and N gene by real-time RT-PCR assay and expressed in cycle threshold (Ct) (Shanghai ZJ Bio-Tech Co., Ltd. Shanghai JN Bio-Tech Co., Ltd. China). The viral clearance time of SARS-CoV-2 was defined as the time from illness onset to patients with two consecutive negative real-time RT-PCR results.

All the analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). The authors expressed the continuous variable as mean  $\pm$  standard (normal distribution), or as the medium (quartile) (skewed distribution). Categorical variables were expressed in frequency or as a percentage. Generalised linear models were conducted to assess the relationship between the peripheral lymphocyte count and virus clearance time. Different models were built by adjusting various risk factors. Non-adjusted, mini-adjusted, and multivariable-adjusted models were listed. The peripheral lymphocyte count was transformed into a categorical variable and then calculated the trend for the purpose of sensitivity analysis. The two-sided p-value  $<0.05$  were considered statistically significant.

**Table I: Association of peripheral lymphocyte count with viral clearance time in different models.**

Exposure	Crude Model	Model I	Model II
Peripheral lymphocyte count, $\times 10^9/L$	-3.49 (-5.69, -1.30)	-3.43 (-5.67, -1.19)	-2.79 (-5.21, -0.36)
Peripheral lymphocyte count in Tertile			
Low	Reference	Reference	Reference
Middle	-1.01 (-4.05, 2.02)	-0.90 (-3.95, 2.15)	-2.48 (-5.35, 0.39)
High	-3.40 (-6.42, -0.37)	-3.33 (-6.40, -0.25)	-3.11 (-6.23, 0.02)
p for trend	0.028	0.035	0.046

Crude Model, no covariates were adjusted. Model I model adjusted for age and gender. Model II model adjusted for gender, age, BMI, fever, disease severity, Ct-values of N, comorbidities, time from illness onset to hospital admission, vaccination, interleukin-6 (IL-6), C-reactive protein, D-dimer, AST, TG, HDL, albumin, serum IgM, serum SARS-CoV-2 antibody, and neutralising antibodies were adjusted.

A total of 202 patients were chosen for the last data analysis after checking by inclusion and exclusion criteria. The patients' mean age was  $41.39 \pm 12.47$  years. Male was accounted for 48.51% and female was 51.49% respectively. The average viral clearance time was  $19.40 \pm 9.03$  days. The covariates adjusted in multiple linear regression were classified as demographic data based on clinical experiences and on the basis of their associations with the viral clearance time or a change in effect estimate of more than 10%. So, the covariates included: gender, age, body mass index (BMI), fever, disease severity, Ct-values of N, comorbidities, time from illness onset to hospital admission, vaccination, interleukin-6 (IL-6), C-reactive protein, D-dimer, aspartate aminotransferase (AST), triglyceride (TG),

high-density lipoprotein (HDL), albumin, serum IgM, serum SARS-CoV-2 antibody, and neutralising antibodies.

Three models were built to analyse the effects of peripheral lymphocyte count on viral clearance time (Table I). In model II, a negative association between peripheral lymphocyte count and viral clearance time ( $\beta$ , -2.79; 95% CI, -5.21 to -0.36) was found. The peripheral lymphocyte count was converted from a continuous to a categorical variable (tertile of peripheral lymphocyte count) for sensitivity analysis. The effect sizes of middle and high tertile of peripheral lymphocyte count were negative in three models, which were consistent with the results when the peripheral lymphocyte count was treated as a continuous variable. The p-value for trend of peripheral lymphocyte count treated as categorical variables in the three models was also consistent with the result when peripheral lymphocyte count was treated as a continuous variable (all  $p < 0.05$ ).

These findings show peripheral lymphocyte count is negatively associated with viral clearance time after adjusting other covariates ( $\beta$ , -2.79; 95% CI, -5.21 to -0.36). Meanwhile, the result was still robust when the authors treated the peripheral lymphocyte count as a categorical variable for calculation. The evidence suggests peripheral lymphocyte count results in an increase in viral clearance of SARS-CoV-2. A prospective study with a large sample size is necessary to further explore the association.

#### ETHICAL APPROVAL:

The study was approved by the Research Ethics Commission of the First Affiliated Hospital of Xiamen University, and the clinical data used in the research was granted permission by the Research Ethics Commission of the First Affiliated Hospital of Xiamen University (No. M2021069).

#### PATIENTS' CONSENT:

Written informed consent was waived in this study because of the nature of a retrospective cohort study.

#### COMPETING INTEREST:

The authors declared no competing interest.

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#### AUTHORS' CONTRIBUTION:

WL, WW, DW: Conception or design of the work, analysis or interpretation of data for the work.

XY, WL, WW, LJ, YL: Drafting the work or revising it critically for important intellectual content.

All the authors have approved the final version of the manuscript to be published.

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