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Correlations Between Anti-SARS-CoV-2 Titers, CD4$^+$ T-Cell Counts, and COVID-19 Severity

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Abstract

Coronavirus disease 2019 (COVID-19) presents with diverse symptoms ranging from mild to severe. Patients with severe COVID-19 can show impaired humoral and cellular immunity and excessive pro-inflammatory cytokine production. Antibodies are generated against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) due to the activation of the humoral immune system. Molecular-based testing is currently used to diagnose COVID-19. Determining antibody and CD4$^+$ T cell counts can help monitor the antibody response to assess the risk of reinfection and vaccine response. This study aimed to determine the relationships between Aanti-SARS-CoV-2 titer, CD4$^+$ T cell count, and COVID-19 severity. This analytic observational study used a cross-sectional design with consecutive sampling and was conducted at RSUP Prof. Dr. R. D. Kandou Manado Hospital from April to October 2021. It comprised 48 patients with COVID-19. The data were compared using Spearman's rank correlation coefficient (r_s). Anti-SARS-CoV-2 titers were nonsignificantly correlated with COVID-19 severity (r_s = 0.081, p = 0.582) and CD4$^+$ T cell counts (r_s = 0.214, p = 0.145). In contrast, CD4$^+$ T cell counts were significantly negatively correlated with COVID-19 severity (r_s = −0.454, p = 0.001). Anti-SARS-Cov-2 titers cannot be used as an indicator of COVID-19 severity. Moreover, CD4$^+$ T cell counts cannot be used as a marker of anti-SARS-CoV-2 titers. However, COVID-19 severity correlates negatively with CD4$^+$ T cell counts, indicating that CD4$^+$ T cell counts can be used as an indicator of COVID-19 severity.

Keywords: Anti-SARS-CoV-2 antibody; CD4$^+$; COVID-19 severity; T cells.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disorder caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a beta-coronavirus with a single-stranded RNA genome. COVID-19 is associated with diverse symptoms ranging from mild to severe, increasing the likelihood of requiring intensive care. SARS-CoV-2 infection causes rapid immune system activation, followed by the clearance of infected cells. Ineffective viral clearance leads innate and adaptive immune cells to accumulate at the site of infection, resulting in immune system hyperactivation and serious complications such as acute respiratory distress syndrome (Bonny et al., 2021; Hojyo et al., 2020; Kutsuna et al., 2021).

Previous research has shown that patients with severe COVID-19 have impaired humoral and cellular immunity and upregulated pro-inflammatory cytokines. Antibodies against SARS-CoV-2 are generated due to the activation of the humoral immune system. COVID-19 is currently diagnosed based on molecular testing, while prior infections are detected based on serological testing for antibodies specific to SARS-CoV-2. While most serological testing is qualitative, quantitative serological assays are needed to evaluate antibodies against the SARS-CoV-2 spike (S) protein. In addition, cellular immune reactions involving CD4 molecule (CD4)$^+$ T cells are crucial in coordinating immune responses by producing neutralizing antibodies with the support of B cells. These cells stimulate cluster of differentiation 8 (CD8)$^+$ T cell activity and memory B and T cell formation. SARS-CoV-2-specific CD4$^+$ T cells produce interleukin 2 (IL2) and interferon-gamma (IFNG), indicating that those recovering from COVID-19 have a T helper 1 cell response (Agra Bermejo et al., 2018; Higgins et al., 2021).

SARS-CoV-2 infection evokes an immune response to the virus in the host, including producing specific antibodies against viral antigens. While patients with COVID-19 show considerable variability in antibody levels and chronological appearance, seroconversion typically occurs two weeks after SARS-CoV-2 infection (Afzal et al., 2021; Higgins et al., 2021). Quantitative antibody and CD4$^+$ T cell counts can help monitor antibody responses longitudinally to assess reinfection

risk, including antibody responses to vaccines. These two tests can be used as prognostic markers for cytokine storms and to determine therapeutic options and COVID-19 severity (Liu et al., 2020). Therefore, this study examined the correlations between COVID-19 severity, anti-SARS-CoV-2 titers, and $CD4^+$ T cell counts.

PATIENTS AND METHODS

Study design and participants

This analytical observational study used a cross-sectional design with consecutive sampling to collect data from the anamnesis, physical examination, and medical records of patients with COVID-19 admitted to RUSP Prof Dr. R.D. Kandou Manado Hospital, Manado, Indonesia, from April to October 2021. Data were collected systematically on adult inpatients (aged >18 years) with COVID-19 confirmed using reverse transcriptase-polymerase chain reaction (RT-PCR) testing of throat swabs. Patients with HIV, autoimmune diseases, malignancy, or who had received a vaccine against SARS-CoV-2 were excluded from this study. All patients who participated in this study or their families were asked to sign an informed consent form.

Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine at Universitas Sam Ratulangi (Ref. Number: No.172/EC/KEPK-KANDOU/X/2021).

Study definition

COVID-19 infection was defined as a positive RT-PCR result from a nasopharyngeal or throat swab. The anti-SARS-Cov-2 titer was defined as the in vitro titer of antibodies (including immunoglobulin G [IgG]) against the receptor binding domain of the SARS-CoV-2 S protein in venous blood samples collected to quantitatively assess the adaptive humoral immune response. The test was conducted using the electro-chemiluminescence immunoassay method, and the positive or reactive cut-off was ≥0.8 U/mL (Mazzoni et al., 2020). The $CD4^+$ T cell count is one of the important indicators used to assess cellular immunity and is obtained via immunoserology. This test was conducted using the flow cytometry method, (Dieye et al., 2011) and the normal reference value for the $CD4^+$ T cell count is 500–1500 cells/mm^3. COVID-19 severity was assessed based on the Quick COVID-19 Severity Index (qCSI) calculated based on the criteria in Table 1. A qCSI of ≤3 is considered low, 4–6 is considered low-intermediate, 7–9 is considered high-intermediate, and 10–12 is considered high (Haimovich et al., 2020).

Table 1. The variables used to calculate the qCSI.

Variable		Points
Respiratory rate, breaths/min	≤22	0
	23–28	1
	>28	2
Pulse oximetry	>92%	0
	89%–92%	2
	≤88%	5
O_2 flow rate, L/min	≤2	0
	3–4	4
	5–6	5

Sample size and data collection

The sample size was estimated considering a 95% confidence level and a 5% prediction error based on the prevalence of COVID-19 infection at the time this study was designed. A sample size of 48 was established.

Outcome measurement

The outcomes measured in this study were the correlations between anti-SARS-CoV-2 titers and qCSI, between $CD4^+$ T cell counts and qCSI, and between anti-SARS-Cov-2 titers and $CD4^+$ T cell counts.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 25.0; IBM Corp., Armonk, NY, USA). The data were tested for normality using the Shapiro–Wilk test since this study included fewer than 50 participants. Since these tests indicated that the data were non-normally distributed, correlations were assessed using Spearman's rank correlation coefficient (r_s). A $p < 0.05$ was considered statistically significant.

RESULTS

This study included 48 outpatients and inpatients aged >18 years with a confirmed COVID-19 diagnosis. The participants' demographic and clinical characteristics (qCSI, anti-SARS-Cov-2 titer, and $CD4^+$ T cell count) are shown in Table 2. Based on the Shapiro–Wilk test, all the data were non-normally distributed ($p < 0.05$).

Table 2. Study subjects' characteristics.

	N = 48	%	Min	Max	Median
Sex					
Male	22	45.8			
Female	26	54.2			
Age (years)	48		21	75	53.50
qCSI					
Low	8	16.7			
Low-Intermediate	25	52.1			
Intermediate-High	10	20.8			
High	5	10.4			
Respiratory rate (breaths/min)	48		14	35	22.5
O_2 saturation	48		86	99	95
O_2 support (lpm)	48		4	15	10
$CD4^+$ T cell count (U/mL)	48		2	1556	486.5
Anti-SARS-CoV-2 titer (U/mL)	48		0	259	159.7

N = the number of samples, Min = minimum, Max = maximum, lpm = liter per minute, U/mL = units per milliliter.

The 48 participants comprised 26 (54%) females and 22 (46%) males with a median age of 53.5 (21–75) years. Based on the qCSI, most (52.1%) were in the low-intermediate category, with only five (10.4%) in the high category. Their median respiratory rate was 22.55 (14–35) breaths per minute. Their mean O_2 support was 10 (4–15) liters per minute. Their median $CD4^+$ T cell count was 486.5 (2–1556) U/mL.

Table 3. Pairwise correlations between variables.

Comparison	*N*	r_s	*p*
Anti-SARS-CoV-2 titer vs. qCSI	48	0.081	0.582
$CD4^+$ T cell count vs. qCSI	48	−0.454	0.001
Anti-SARS-CoV-2 titer vs. $CD4^+$ T cell count	48	0.214	0.145

A bivariate analysis of the variables is shown in **Table 3**. Anti-SARS-CoV-2 titer was not significantly correlated with qCSI (rs = 0.081, $p = 0.582$). In contrast, the $CD4^+$ T cell count was significantly negatively correlated with qCSI ($r_s = -0.454$, $p = 0.001$), indicating a significant inverse relationship between the $CD4^+$ T cell count and COVID-19 severity. However, the anti-SARS-CoV-2 titer was not significantly correlated with the $CD4^+$ T cell count ($r_s = 0.214$, $p = 0.145$), indicating no relationship exists between anti-SARS-CoV-2 titers and $CD4^+$ T cell counts in patients with COVID-19.

DISCUSSION

The mean age of the participants in our study was 52.67 ± 13.9 years, consistent with the mean age of patients hospitalized at a Swedish hospital reported by Bläckberg et al (Bläckberg et al., 2021). The age and sex distributions of the participants in our study are also similar to those of the 473 patients with COVID-19 in Xiquan et al. (mean age = 52.5 ± 13.9 years, 54% female) (Yan et al., 2022). Moreover, these demographics are consistent with the 254 patients who tested positive for SARS-CoV-2 in Katharina Röltgen et al (Röltgen et al., 2020).

Most participants in our study had a qCSI in the low-intermediate category (52.1%). Their mean oxygen support was 7.8 ± 5.6 lpm. The COVID-19 severities of the participants in our study were similar to those in Xiquan et al., where most patients with COVID-19 were in the intermediate category (356/473, 75.3%) because that study was conducted on post-hospitalized patients, with a hospitalization period around January to March 2020, when the COVID-19 vaccine was not yet widely available (Yan et al., 2022). In our study, anti-SARS-CoV-2 titers were nonsignificantly correlated with COVID-19 severity, as assessed by the qCSI.

Previous research has identified several factors associated with COVID-19 severity, including SARS-CoV-2 viral load, the ability to neutralize anti-SARS-CoV-2 antibodies, and anti-SARS-CoV-2 antibody titers. SARS-CoV-2 levels were found to fluctuate as the disease progresses (Bonny et al., 2021; Bulut & Kato, 2020; Hojyo et al., 2020; Kutsuna et al., 2021; Sun et al., 2020). Long et al. observed that SARS-CoV-2 IgG titers began to appear on days 17–19 after symptom onset, suggesting that SARS-CoV-2 antibody titers obtained before days 17–19 were insufficient to predict COVID-19 severity (Lee et al., 2021; Long et al., 2020).

Our study found a strong negative correlation between $CD4^+$ T cell counts and COVID-19 severity, indicating that the greater the number of $CD4^+$ T cells,

the less severe COVID-19 is, and vice versa. These findings are consistent with Wang et al., who found that low $CD4^+$ T cell counts were associated with poor radiological outcomes and more severe lung conditions in 162 patients with COVID-19. Therefore, reduced T cell counts appear to be a typical feature of SARS-CoV-2 infection, which is particularly evident in critically ill patients at risk of intensive care unit admission and mortality. Consequently, a decrease in T cells may serve as a warning sign for COVID-19 exacerbation. The exact mechanism by which SARS-CoV-2 infection can cause a decrease in $CD4^+$ T cells remains unknown (Wang et al., 2021). Peng et al. reported that numerous pathways are suspected of causing the decrease in T cells. Direct attacks by SARS-CoV-2 have been shown to harm 50% of circulating lymphocytes, inducing cell death via necrosis, apoptosis, and pyroptosis. In addition, there is an increase in inhibitory cytokines secreted by lung macrophages or infected epithelial cells, including tumor necrosis factor (TNF), which is known to induce T cell apoptosis, interleukin 10 (IL10), which prevents T cell proliferation, and type I interferons, which affect lymphocyte recirculation. However, further research is needed to determine whether these mechanisms contribute to the decrease in $CD4^+$ T cells (Peng et al., 2020).

Our study found that anti-SARS-CoV-2 titers did not correlate significantly with $CD4^+$ T cell counts. This result contrasts with Koblischke et al., who measured antibody and cellular immune responses, which play an important role in viral clearance and disease severity. $CD8^+$ T cell-mediated immunity is an important factor in clearing severe viral infections, and $CD4^+$ T cell counts have been shown to decrease with the worsening COVID-19 (Koblischke et al., 2020). Various factors can influence anti-SARS-CoV-2 titers, including age, COVID-19 treatment, and prior medical history, such as hypertension, kidney disease, chronic obstructive pulmonary disease, and diabetes mellitus (Bläckberg et al., 2021; Chvatal-Medina et al., 2021; Kutsuna et al., 2021).

Our study had several limitations that may have affected its analysis and the interpretation of its results. One limitation was its sampling approach, which used a non-probability method, decreasing its external validity and meaning its results cannot be generalized to the broader population. In addition, its correlation could not identify a causal relationship since they did not consider the time of the examination relative to symptom onset or hospital admission, as well as the patient's basic comorbidities.

CONCLUSIONS

Based on our findings, anti-SARS-CoV-2 titers are not associated with COVID-19 severity, indicating that anti-SARS-CoV-2 titers cannot be used to predict COVID-19 severity. In contrast, $CD4^+$ T cell counts were significantly associated with COVID-19 severity, where the greater the number of $CD4^+$ T cells, the less severe COVID-19 is, and vice versa. Because there is no correlation between $CD4^+$ T cell counts and anti-SARS-CoV-2 titers, $CD4^+$ T cell counts cannot be used as a marker to predict anti-SARS-CoV-2 titers.

Competing Interests: The authors declare that there are no competing interests.

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