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Increased body mass index linked to decreased neutralizing antibody titers of inactivated SARS-CoV-2 vaccine in healthcare workers

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Abstract

Objective: Obesity is an important risk factor for COVID-19. However, whether obesity affects SARS-CoV-2 antibody production is unclear. This study aimed to identify the influence of obesity on neutralizing antibody production of an inactivated SARS-CoV-2 vaccine to better guide vaccination strategies.

Methods: This cross-sectional study recruited a total of 239 healthcare workers (age, 21–50 years) from Suining Central Hospital during 22–23 April 2021. An electronic questionnaire on basic characteristics was completed by all participants. A general physical exam and fasting blood sampling by venipuncture were performed. Peripheral leukocyte counts and the ratios of leukocyte subsets, hepatorenal function, and the neutralizing antibody titers against SARS-CoV-2 were measured.

Results: Among 239 healthcare workers, the participants with underweight, normal weight, overweight, and obesity accounted for 10.88%, 64.44%, 23.01%, and 1.67%, respectively. The highest peripheral monocyte counts were observed in the group with obesity, whereas the lowest were observed in the group with normal weight. Similar results were obtained with respect to percentage of peripheral monocytes. Participants with obesity had higher peripheral eosinophil counts and percentages than the other three groups. The median neutralizing antibody titer was 12.70 AU/mL, with 85.36% (n = 204) of participants were sufficiently protected against SARS-CoV-2. The lowest neutralizing antibody titers were observed in the group with obesity, whereas the highest were observed in the group that was underweight. Additionally, high BMI was significantly associated with high peripheral monocyte counts [B (95% CI) = 0.008 (0.002, 0.013)] and low neutralizing antibody titers [B (95% CI) = −1.934 (−3.663, −0.206)].

Juan Hu and Mingcai Zhao contributed equally as co-first authors.

Conclusions: Obesity could induce chronic inflammation, and associated with lower neutralizing antibody titers against SARS-CoV-2 after inactivated SARS-CoV-2 vaccination.

KEYWORDS
Body mass index, Inactivated SARS-CoV-2 vaccine, Leukocyte, Neutralizing antibody titer

1 | INTRODUCTION

COVID-19, which was first reported in December 2019 and is caused by SARS-CoV-2, has spread rapidly globally. At the time of writing (15 April 2022), more than 500.18 million cases of COVID-19 (including >6.19 million deaths) have been confirmed worldwide.[1–3] Because of the high morbidity and mortality, the COVID-19 pandemic poses an unprecedented risk for global public health and socioeconomic security.[4,5]

Obesity is an important risk factor for COVID-19, increasing the morbidity, severity, and mortality of COVID-19.[6–8] A systematic review indicated that individuals with obesity have a higher risk of COVID-19 positivity, hospitalization, ICU admission, and mortality (odds ratio [OR] = 1.46, 2.13, 1.74, and 1.48, respectively).[9] Another meta-analysis revealed that the mortality OR of COVID-19 patients whose body mass index (BMI) > 25 kg/m^2 was 3.68.[10] In addition, obesity may inhibit B cell function through chronic inflammation, resulting in dysregulated adaptive and innate immunity.[11–13] Obesity might induce an immune imbalance, suppressing antibody production after vaccination, including antibodies against influenza, hepatitis B, tetanus, and rabies.[11,14–16] Currently, whether obesity is associated with lower SARS-CoV-2 antibody production after vaccination is unclear.[9]

To investigate whether obesity affects SARS-CoV-2 antibody production, and guide vaccination strategies toward herd protection, this study assessed peripheral blood inflammatory status and plasma neutralizing antibody titers in healthcare workers who received the second dose of inactivated SARS-CoV-2 vaccine, and further established does-effect-relationships among BMI value, chronic inflammation, and plasma neutralizing antibody titers.

2 | MATERIALS AND METHODS

2.1 | Study participants

This cross-sectional study recruited a total of 239 healthcare workers (age, 21–50 years) from Suining Central Hospital during 22–23 April 2021, including 77 men (age, 22–50 years) and 162 women (age, 21–50 years). All participants received the second dose of inactivated SARS-CoV-2 vaccine (Vero cell, SINOVAC, China) on 10 March 2021, and were free of any known medical condition when biological samples were obtained. An electronic questionnaire on basic characteristics, behavior and dietary habits, night shift frequency, educational level, and family socioeconomic status was completed by all participants.

2.2 | General physical exam and laboratory measurements

A general physical exam (including height and weight) and fasting blood sampling by venipuncture were performed by trained nurses. EDTA anticoagulant (2 mL) was used to analyze peripheral blood cells, and heparin sodium anticoagulant (5 mL) was applied to separate plasma, which was used to estimate neutralizing antibody titers against SARS-CoV-2 and the individual health status, including hepatorenal function and lipid levels. Then, the remainder of the blood and plasma was aliquoted and stored at −80°C.

All procedures were performed in accordance with the International Standardization Organization (ISO) 15189 quality and management requirements. Peripheral leukocyte counts and the ratios of leukocyte subsets were determined by an automatic hematology analyzer (Sysmex XN-9000, Japan) within 1 h after sampling.[17,18] Plasma was separated by centrifugation (3500 rpm, 5 min) at room temperature. Hepatorenal function was assessed based on the aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), uric acid, urea, creatinine, and cystatin C levels. Simultaneously, the total cholesterol, triglycerides, high-density lipoprotein–cholesterol (HDL-C), and low-density lipoprotein–cholesterol (LDL-C) levels were measured. All data were recorded by an automatic biochemical analyzer (Hitachi LST 7600, Japan).[18,19] In addition, an automatic chemiluminescence immunoassay analyzer (Maccura i 3000, China) was used to assess the neutralizing antibody titers against SARS-CoV-2.[18]

2.3 | Ethics approval and informed consent

This study was approved by the Medical Research Ethics Committee of Suining Central Hospital, China (LLSNCH20210012). All participants signed informed consent prior to participation.

2.4 | Statistical analysis

BMI values were calculated, and participants were divided into four groups according to Chinese BMI criteria.[20] BMI < 18.5 kg/m^2 was defined as underweight, 18.5 kg/m^2 ≤ BMI < 24 kg/m^2 was defined as normal weight, 24 kg/m^2 ≤ BMI < 28 kg/m^2 was defined as overweight, and BMI ≥ 28 kg/m^2 was defined as having obesity. The Kolmogorov–Smirnov test was performed to estimate

data distribution characteristics. Normally distributed data are presented as mean and standard deviation (SD), and non-normally distributed data are shown as median and interquartile range (IQR).

To identify differences in systemic inflammation and neutralizing antibody titers between groups, one-way ANOVA and the Kruskal–Wallis test were performed depending on data distributions. The Spearman rank correlation test was conducted to identify the factors associated with BMI. Finally, to estimate the relationships between BMI, systemic inflammation, and neutralizing antibody titer, the Pearson correlation test and a multivariable adjusted linear regression model were applied. Covariates included basic characteristics, behavior and dietary habits, night shift frequency, educational level, and family socioeconomic status.[21] SPSS (version 22.0; IBM, USA) was used to analyze the data, and GraphPad Prism (version 8.0; GraphPad, CA) was used to edit the figures. A two-tailed p-value of <0.05 was defined as the limit of statistical significance.

3 | RESULTS

A total of 239 healthcare workers were recruited in this cross-sectional study (Table 1). The median (IQR) age was 31 (27, 36) years old, and the ratio of gender was 77/162 (male/female). The mean BMI was 21.81 kg/m^2. Participants with underweight, normal weight, overweight, and obesity accounted for 10.88%, 64.44%, 23.01%, and 1.67%, respectively. The median daily sleeping time was 7 h, and most participants spent more than 2 h per day outside. Most participants did not smoke cigarettes (80.03%) or consume alcohol (70.71%). About 78% of participants had a bachelor degree or above, and 50.63% of participants had a monthly household income below 10,000 yuan (ranging from 1500 to 1600 US dollars). Hepatorenal function and lipid levels were assessed, and the following median or mean plasma concentrations were obtained: AST, 21 U/L; ALT, 14 U/L; GGT, 19 U/L; ALP, 64 U/L; uric acid, 314 μM; urea, 5.31 mM; creatinine, 59 μM; cystatin C, 0.76 mg/L; total cholesterol, 4.65 mM; triglycerides, 1.32 mM; HDL-C, 1.23 mM; LDL-C, 2.48 mM, and all values were within the biological reference range.

Although the difference in peripheral white blood cell (WBC) counts between groups was not significant ($p > 0.05$), significant differences in peripheral monocyte counts and eosinophil counts were observed, with the highest peripheral monocyte counts and eosinophil counts in the group with obesity and the lowest in the group that was underweight (all $p < 0.05$; Figure 1). Similar results were obtained in the percentages of peripheral monocytes and eosinophils (all $p < 0.05$; Figure 1). The highest neutralizing antibody titers were found in the group that was underweight, whereas the lowest in the group with obesity ($p < 0.05$; Figure 2). The median neutralizing antibody titer was 12.70 AU/mL, with 85.36% ($n = 204$) participants having a neutralizing antibody titer of ≥6 AU/mL (the reference range provided by the manufacturer;

TABLE 1 General characteristics and health data of 239 healthcare workers

Variable	Health data
Gender (male/female)	77/162
Age [median (IQR), years]	31.00 (27.00, 36.00)
Height [median (IQR), m]	1.62 (1.58, 1.69)
Weight [median (IQR), kg]	56.00 (50.00, 65.00)
BMI (mean ± SD, kg/m^2)	21.81 ± 2.83
Daily outdoor time [*n* (%), hour]	
≤1	47 (19.67)
1–2	83 (34.73)
2–3	42 (17.57)
>3	67 (28.03)
Daily sleeping time [median (IQR), hour]	7.00 (7.00, 8.00)
Cigarette smoking (yes/no)	31/208
Alcohol drinking (yes/no)	70/169
Night shift frequency [*n* (%)]	
Occasionally or none	74 (30.96)
2 weeks-1 month per 1 time	18 (7.53)
Once a week	59 (24.69)
At least twice a week	88 (36.82)
Educational level [*n* (%)]	
College	53 (22.18)
Bachelor	154 (64.43)
Master/doctor	32 (13.39)
Monthly household income [*n* (%), yuan]	
<10,000	121 (50.63)
10,000–15,000	70 (29.29)
>15,000	48 (20.08)
AST [median (IQR), U/L]	21.00 (18.00, 25.00)
ALT [median (IQR), U/L]	14.00 (10.00, 23.00)
GGT [Median (IQR), U/L]	19.00 (14.00, 28.00)
ALP [median (IQR), U/L]	64.00 (56.00, 80.00)
Total cholesterol (mean ± SD, mM)	4.65 ± 0.84
Triglycerides [median (IQR), mM]	1.32 (0.93, 2.13)
HDL-C (mean ± SD, mM)	1.23 ± 0.31
LDL-C (mean ± SD, mM)	2.48 ± 0.64
Uric acid [median (IQR), uM]	314.00 (261.00, 395.00)
Urea (mean ± SD, mM)	5.31 ± 1.16
Creatinine [median (IQR), uM]	59.00 (52.00, 75.00)
Cystatin C (mean ± SD, mg/L)	0.76 ± 0.11

Abbreviations: ALP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; BMI, body mass index; GGT, gamma glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

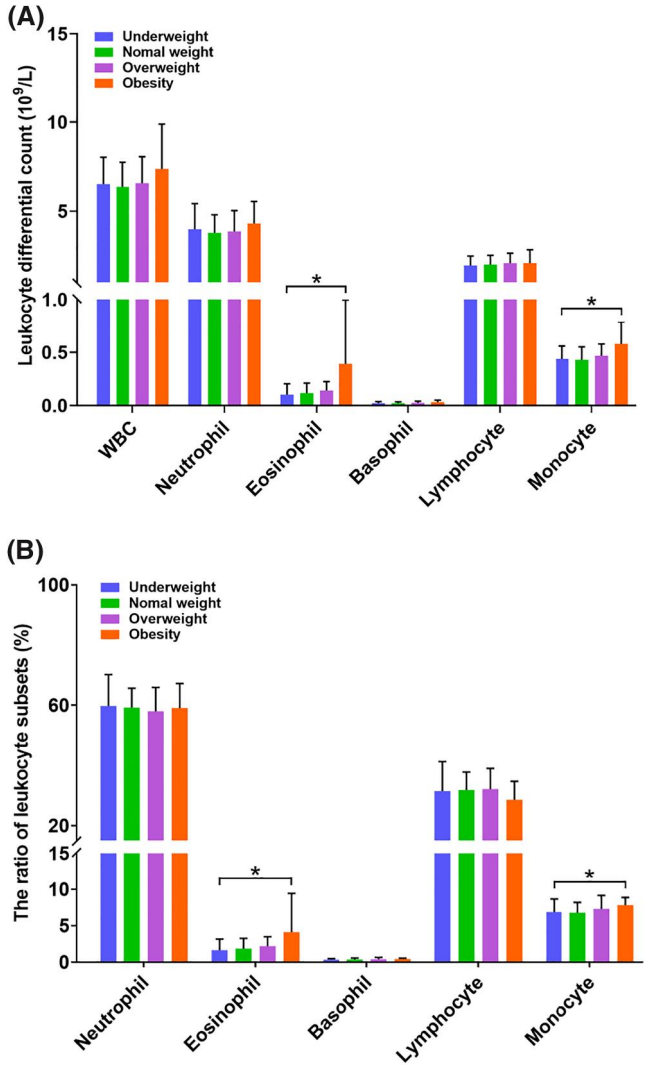

FIGURE 1 Peripheral leukocyte counts and the percentages of leukocyte subsets in participants. Data are presented as mean ± standard deviation, $^{*}p < 0.05$

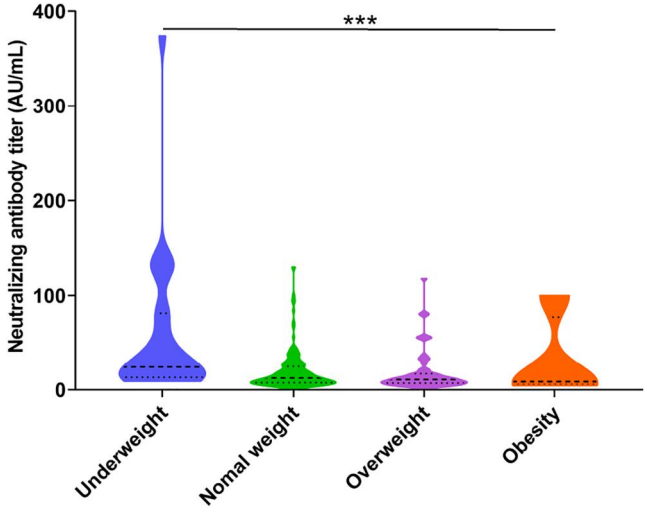

FIGURE 2 Neutralizing andibody titer of against SARS-CoV-2 in participants. Data are presented as median (interquartile range), $^{***}p < 0.001$

Vero cell, SINOVAC, China), indicating 85.36% of healthcare workers maybe sufficiently protected against SARS-CoV-2.

Spearman rank correlation analysis was performed to identify factors associated with BMI. BMI was positively associated with age, daily outdoor time, cigarette smoking, and drinking alcohol ($r_s = 0.281$, $r_s = 0.132$, $r_s = 0.165$, and $r_s = 0.265$, respectively, all $p < 0.05$), whereas BMI was negatively correlated with the gender ($r_s = -0.354$, $p < 0.001$; Figure 3). Although the counts of peripheral leukocytes and leukocyte subsets were all positively associated with individual BMI, statistical significance was only observed for peripheral eosinophil counts, monocyte counts, and monocyte percentage ($r_s = 0.146$, $r_s = 0.225$, and $r_s = 0.174$, respectively, all $p < 0.05$; Table S1). Additionally, neutralizing antibody titers were negatively associated with individual BMI ($r_s = -0.171$, $p < 0.01$; Table S1).

To further identify the dose-respondent relationships among BMI, systemic inflammation, and neutralizing antibody titers, multivariable adjusted linear regression analysis was conducted (Figure 4). In the unadjusted model, increased BMI was significantly associated with increased levels of chronic inflammatory biomarkers (including peripheral monocyte counts, eosinophil counts, and monocyte percentage) and decreased neutralizing antibody titers [B = 0.010, 0.006, 0.096, and −2.106; 95% confidence interval (CI): (0.004, 0.015), (0.001, 0.012), (0.027, 0.166), and (−3.657, −0.555), respectively, all $p < 0.05$]. After further adjusting for covariates (including age, gender, daily outdoor time, daily sleeping time, cigarette smoking, drinking alcohol, night shift frequency, educational level, and monthly household income), the correlation remained significant for peripheral monocyte counts and neutralizing antibody titers [B (95% CI): 0.008 (0.002, 0.013), and −1.934 (−3.663, −0.206), respectively, all $p < 0.05$]. These results indicated that with one unit increment in BMI, the peripheral monocyte count increases on average with 0.008 10^9/L and the neutralizing antibody titer decreases on average with 1.934 AU/mL.

4 | DISCUSSION

This cross-sectional study found that participants with obesity have increased peripheral monocyte counts and percentages, elevated peripheral eosinophil counts and percentages, and decreased neutralizing antibody titers compared to the other three groups. Individual BMI is positively associated with peripheral monocyte counts, but negatively associated with the neutralizing antibody titer. This study suggests that healthcare workers with obesity may suffer from chronic systemic inflammation and hence produce lower levels of neutralizing antibody against SARS-CoV-2 after vaccination.

Peripheral monocytes play a pivotal immune-regulatory role and serve as biomarkers for chronic inflammation.[17,22] In the present study, participants with obesity and overweight had higher peripheral monocyte counts (mean: 0.58 × 10^9/L and 0.47 × 10^9/L, respectively) and higher percentages of peripheral monocytes (mean: 7.83% and 7.32%, respectively) than participants with normal weight (mean: 0.43 × 10^9/L and 6.79%). Higher BMI is associated with elevated peripheral monocyte counts. These results are consistent

with prior studies that indicated obesity is associated with increased mononuclear macrophage recruitment, inducing chronic inflammation.[8,11–13] Similar to aging, obesity could lead to systemic inflammation through chronic systemic immune activation.[14] In vitro cell culture experiments showed that B cells from individuals with obesity produce higher interleukin-6 (IL-6) and lower IL-10 levels.[12]

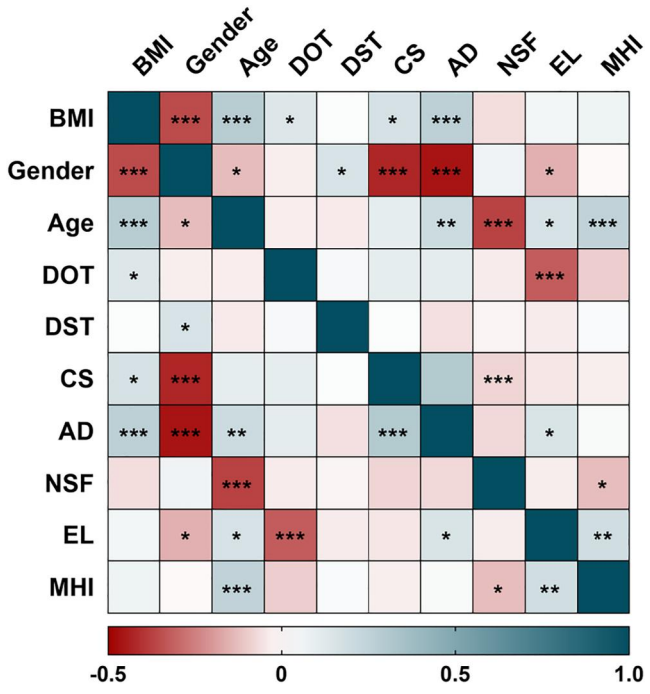

FIGURE 3 Spearman rank correlations (r_s) of individual BMI and associated factors. AD, alcohol drinking; BMI, body mass index; CS, cigarette smoking; DOT, daily outdoor time; DST, daily sleeping time; EL, educational level; MHI, monthly household income; NSF, night shift frequency; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Obesity was associated with higher counts of pro-inflammatory macrophages, which could further promote inflammation.[14] In summary, this study indicated that high BMI is associated with increased chronic inflammation in healthcare workers.

Concurrently, in this study, the lowest neutralizing antibody titers were found in the group with obesity (median: 8.60 AU/mL) and the highest titers were found in the group that was underweight (median: 24.41 AU/mL). Moreover, neutralizing antibody titers were negatively associated with BMI. Previous studies suggested that individuals with obesity have an impaired immune function, resulting in a poor response to hepatitis B, influenza, rabies, and tetanus vaccination.[14,15] Sheridan et al.[16] demonstrated that obesity was associated with lower $CD8^+$ T cell counts in humans, suggesting obesity may reduce the protective effects of vaccination against influenza. The studies by Frasca et al.[12,13] suggested that obesity could decrease B cell function and increase the number of pro-inflammatory B cells and that obesity-related chronic inflammation could weaken both innate and adaptive immune responses. Therefore, obesity may be associated with a reduced immune response to SARS-CoV-2 vaccination due to chronic inflammation, resulting in lower neutralizing antibody titers.

Based on the manufacturer's specifications (Vero cell, SINOVAC, China), 85.36% of healthcare workers were protected (antibody titer ≥6 AU/mL) after vaccination with the inactivated SARS-CoV-2 vaccine. The neutralizing antibodies could protect individuals against SARS-CoV-2 infection.[23,24] A population-based cross-sectional study in Wuhan, China showed that pan-immunoglobulins against SARS-CoV-2 were detected in only 6.92% of recovered patients; 39.8% of recovered patients were positive for neutralizing antibodies.[4] Recently, a randomized clinical trial indicated that the efficacies of two inactivated SARS-CoV-2 vaccines (WIV04 and HB02, China National Biotec Group Co., Ltd.) were 72.8% and

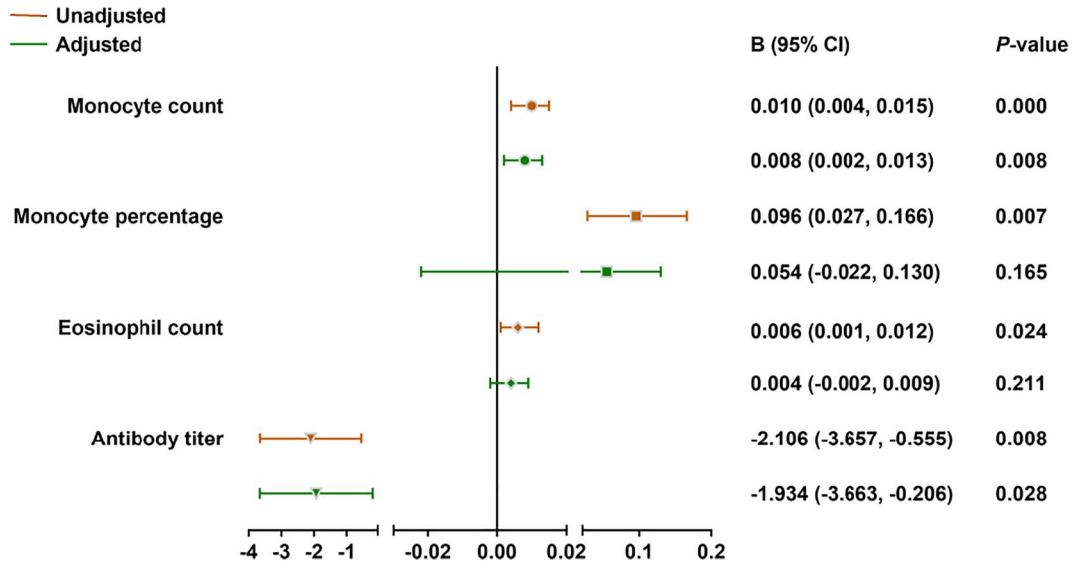

FIGURE 4 The associations of individual BMI with chronic inflammation and neutralizing antibody titer. Adjusted for age, gender, daily outdoor time, daily sleeping time, cigarette smoking, alcohol drinking, night shift frequency, educational level, and monthly household income; Statistical significance, $p < 0.05$

78.1%, respectively.[25] These inconsistencies can be due to differences in participants and vaccines. Indeed, this study was performed in Chinese healthcare workers, and the other studies were conducted in COVID-19 patients (Wuhan, China) or West Asian adults.

The present study revealed that obesity is related with chronic inflammation and suppression of neutralizing antibody production after inactivated SARS-CoV-2 vaccination and the protective efficacy of the inactivated SARS-CoV-2 vaccine (Vero cell, SINOVAC, China) among healthcare workers was 85.36%.

A limitation of the present cross-sectional study is that it was conducted only among healthcare workers, so the relationship between BMI and neutralizing antibody titer might be overestimated. Nevertheless, the present study provides valuable insights that can help to guide vaccination strategies and obtain herd immunity, in order to stop the global COVID-19 pandemic.

5 | CONCLUSION

In summary, this cross-sectional study estimated the relationships among BMI, chronic inflammation, and neutralizing antibody titers after vaccination with an inactivated SARS-CoV-2 vaccine. The results suggest that individuals with obesity had increased peripheral monocyte counts and percentages, elevated peripheral eosinophil counts and percentages, and decreased neutralizing antibody titers. BMI is positively associated with peripheral monocyte counts, but negatively associated with neutralizing antibody titers. In short, these results support the hypothesis that obesity can induce chronic inflammation, resulting in a poor response to the inactivated SARS-CoV-2 vaccine, ultimately decreasing neutralizing antibody titers against SARS-CoV-2. Therefore, BMI values should be considered in future vaccination programs.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY

All data generated or analyzed are included in this published article and supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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