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RESEARCH ARTICLE

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A potential association between obesity and reduced effectiveness of COVID-19 vaccine-induced neutralizing humoral immunity

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Abstract

Due to the adverse effects of obesity on host immunity, this study investigated the effectiveness of COVID-19 vaccines (BNT162b2, ChAdOx-nCov-2019, and mRNA-1273) in inducing anti-SARS-CoV-2 Spike (S) neutralizing antibodies among individuals with various obesity classes (class I, II, III, and super obesity). Sera from vaccinated obese individuals ($n = 73$) and normal BMI controls ($n = 46$) were subjected to S-based enzyme-linked immunosorbent assay (ELISA) and serum-neutralization test (SNT) to determine the prevalence and titer of anti-SARS-CoV-2 neutralizing antibodies. Nucleocapsid-ELISA was also utilized to distinguish between immunity acquired via vaccination only versus vaccination plus recovery from infection. Data were linked to participant demographics including age, gender, past COVID-19 diagnosis, and COVID-19 vaccination profile. S-based ELISA demonstrated high seroprevalence rates (>97%) in the study and control groups whether samples with evidence of past infection were included or excluded. Interestingly, however, SNT demonstrated a slightly significant reduction in both the rate and titer of anti-SARS-CoV-2 neutralizing antibodies among vaccinated obese individuals (60/73; 82.19%) compared to controls (45/46; 97.83%). The observed reduction in COVID-19 vaccine-induced neutralizing humoral immunity among obese individuals occurs independently of gender, recovery from past infection, and period from last vaccination. Our data suggest that COVID-19 vaccines are highly effective in inducing protective humoral immunity. This effectiveness, however, is potentially reduced among obese individuals which highlight the importance of booster doses to improve their neutralizing immunity. Further investigations on larger sample size remain necessary to comprehensively conclude about the effect of obesity on COVID-19 vaccine effectiveness on humoral immunity induction.

KEYWORDS

COVID-19 vaccine, ELISA, humoral immunity, mRNA vaccine, obesity, SARS-CoV-2

Arwa A. Faizo and Fadi S. Qashqari contributed equally to this study.

1 | INTRODUCTION

Obesity is the leading metabolic disease in the 21st Century.[1] It is now recognized as a worldwide pandemic affecting both genders of all age groups.[2,3] Increased morbidity and mortality are associated with obesity and its related impaired metabolic health complications such as insulin resistance, diabetes mellitus, hyperlipidemia, hypercholesterolemia, endothelial dysfunction, and cardiovascular disorders.[4] Individuals with obesity confers a state of low-grade inflammation as evidenced by increased peripheral white leukocyte count, and induction of cytokine and chemokine secretion.[5] The primary site of this inflammatory response is adipose tissues, but its effects can extend to other sites of the body.[5,6] Several process may contribute to the subclinical inflammatory state of individuals with obesity. These include accumulation of reactive oxygen species, poor oxygen consumption, low oxygen tension, and induction of endoplasmic reticulum stress.[7,8] These preexisting states can make obese people more vulnerable to some viruses particularly those who utilize these mechanisms to promote viral pathogenesis.[9,10]

With the ongoing COVID-19 pandemic, several studies demonstrated obesity as a risk factor to develop severe COVID-19 symptoms and complications (e.g., hospitalization, intensive care unit admission, requirement of mechanical ventilation, and death).[11–14] Interestingly, this occurs independently of other factors that are usually tightly related to obesity (e.g., diabetes mellitus and cardiovascular disorders). It is not entirely clear how increased BMI may promote adverse COVID-19 outcomes. However, impaired production of proinflammatory cytokines, infiltration of innate immune cells, and suppression of T and B lymphocyte functions may contribute to viral-induced immunopathology, uncontrolled pulmonary inflammation, and respiratory tissue damage.[15–18] Hyperglycemia and hyperinsulinemia in obese people were found to reduce the inflammatory potential and promote the immunosenescence of the CD4 and CD8 compartments which may render these individuals more vulnerable to the infection.[15–18] Hyperinsulinemia can also promote the viral uptake in adipocytes by upregulating the expression of GRP78 which serves as a binding cofactor of the viral spike (S) and the cellular receptor ACE2.[15–18] Thereby, several reports recommended prioritization of obese people to obtain COVID-19 vaccination.[11,19,20]

However, because of the adverse effects of obesity and its tightly related condition diabetes mellitus on host immunity, there is a concern about the effectiveness of COVID-19 vaccines among obese people.[13,14,20,21] In fact, this issue is not unique to COVID-19 vaccinations, as previous reports demonstrated obesity-associated reduction of vaccine effectiveness to other viral infections (e.g., influenza and hepatitis B viruses).[22,23] To our best of knowledge, there is currently a lack of focused reports about this issue in COVID-19 vaccination settings. Some previous studies had obese individuals among their study population, but these studies did not intensively investigate whether obesity affects COVID-19 vaccine effectiveness.[24–28] Moreover, immunoassays that only determine the presence of anti-SARS-CoV-2 antibodies, but do not assess their neutralizing activity, were utilized in most of these studies. Hence, we aimed to investigate the effectiveness of various S-based COVID-19 vaccines in inducing anti-S IgG antibodies among individuals with various classes of obesity (class I, II, III, and super obesity). The neutralizing activity of these antibodies was determined by serum-neturalization test (SNT) utilizing a local SARS-CoV-2 isolate. Anti-nucleocapsid (NP) was also assessed, in addition to obtaining participants' history of past COVID-19 molecular diagnosis, to differentiate between acquired immunity via vaccination only or though vaccination and recovery from past infection.

2 | MATERIALS AND METHODS

2.1 | Clinical samples

This study aimed to investigate the effectiveness of COVID-19 vaccines among individuals older than 18 with obesity (BMI ≥ 30 kg/m^2) who received two doses of COVID-19 vaccine. To provide a side-by-side comparison, those with normal BMI were also invited to participate in the study. Voluntary participants were asked to sign an informed consent, fill in a questionnaire, and provide a serum sample. The questionnaire included questions about participant demographics such as age, gender, height, weight, past COVID-19 confirmed diagnosis by PCR, COVID-19 vaccination history including vaccination dates, types, and number of doses.

2.2 | Laboratory investigations

We have previously developed two in-house enzyme-linked immunosorbent assay (ELISA) protocols that enable detection of Human IgG directed to SARS-CoV-2 spike and NP proteins. Both assays offered up to 100% sensitivity and ≥98.4% specificity.[29–31] The cut-off optical density values at 450 nm for the S and NP assays are 0.27 and 0.17, respectively.[29,30] All sera collected in this study were screened for the presence of SARS-CoV-2 specific antibodies utilizing these in-house ELISAs. The neutralizing activity was assessed by SNT utilizing the local SARS-CoV-2 isolate (SARS-CoV-2/human/SAU/85791C/2020, gene bank accession number: MT630432). All SNT experiments were conducted in biosafety containment level 3. Samples with SN titer of ≥1:20 were considered positive.[29,30]

2.3 | Statistical analyses and data curation

Figure drawing and statistical analysis were performed using GraphPad Prism software version 9.0.2 (GraphPad Software). Fisher's exact, Kruskal–Wallis test, and Mann–Whitney *U* tests were applied as appropriate with $p \leq 0.05$ considered statistically significant.

3 | RESULTS

A total of 119 serum samples were collected from participants. Of these, 73 participants belonged to participants with various classes of obesity (class I, II, III, and super obesity). Their BMI ranged from 30.12 to 64.93 kg/m.^{2} Their ages ranged from 18 to >60 years. The study group included 41 (56.2%) male and 32 (43.2%) female participants. All participants received two doses either of a single COVID-19 vaccine type (homologous) or a mixture of two COVID-19 vaccine types (heterologous). Participants in the study group were subgrouped based on the duration between second dose of vaccination and sample collection to <90 (16, 21.9%), 91–180 (45, 61.6%), and >180 days (12, 16.5%). Some participants were previously diagnosed with COVID-19 by RT-PCR (16/73; 21.9%).

The control group comprised 46 samples from normal BMI (18–25 kg/m^2) individuals aged between 18 and 39 years old, the control group included 16 (34.8%) male and 30 (65.2%) female participants. All control group participants received two doses of homologous or heterologous COVID-19 vaccination and were subgrouped based on the duration between second dose of vaccination and sample collection to <90 (27, 58.7%), 91–180 (14, 30.4%), and >180 days (5, 10.9%). Ten out of 46 (21.7%) were previously diagnosed with COVID-19. Demographic and clinical data of study and control groups are shown in Table 1.

All samples were subjected to in house ELISAs that enable sensitive and specific detection of human IgG antibodies directed against either SARS-CoV-2 S or NP antigen.[29–31] It is important to note that all participants have received two doses of homologous or heterologous doses of the following COVID-19 vaccines: BNT162b2 by Pfizer-BioNTech, ChAdOx nCov-2019 by AstraZeneca, or mRNA-1273 by Moderna. All three vaccine types mount host immune response exclusively to SARS-CoV-2 S protein. Hence, S-based ELISA was utilized to determine the presence of human IgG to S antigen. Among the 119 samples, 117 (98.32%) tested positive by S-based ELISA with OD450 values >0.27. The sero-positivity rates were 98.63% (72/73) and 97.83% (45/46) in study (obese) and control (normal BMI) groups, respectively (odd ratio = 1.6; 95% confidence interval [CI] = 0.08253–30.77; $p > 0.99$ (Figure 1A,B).

To accurately estimate the vaccine effectiveness, it was important to identify any recovered cases and, therefore, NP-based ELISA

TABLE 1 Study population categorized as per gender, age group, past COVID-19 diagnosis, type of vaccine received, and obesity class

		Control group normal BMI (*n* = 46)		Study group obese (*n* = 73)	
Catagory	**Subcategory**	***n***	**%**	***n***	**%**
Gender	Male	16	34.8	41	56.2
	Female	30	65.2	32	43.8
Age	18–39	46	100	33	45.2
	40–59			28	38.4
	>60			12	16.4
Obesity status	Normal (BMI 18–25)	46	100		
	Class I (BMI 30–34.99)			7	9.6
	Class II (BMI 35–39.99)			10	13.7
	Class III (BMI 40–49.99)			34	46.6
	Super obesity (BMI > 50)			22	30.1
Past COVID-19 diagnosis	Yes	10	21.7	16	21.9
	No	36	78.3	57	78.1
COVID-19 vaccination	Two doses of BNT162b2	38	82.6	31	42.5
	Two doses of ChAdOx nCov-2019	3	6.5	17	23.3
	Mixed doses of BNT162b2 and ChAdOx nCov-2019	5	10.9	18	24.7
	Mixed doses of BNT162b2 and mRNA-1273			5	6.8
	Mixed doses of ChAdOx nCov-2019 and mRNA-1273			2	2.7
Period from last vaccination (days)	<90	27	58.7	16	21.9
	91–180	14	30.4	45	61.6
	>180	5	10.9	12	16.5

Note: Numbers (*n*) and percentages (%) are shown.

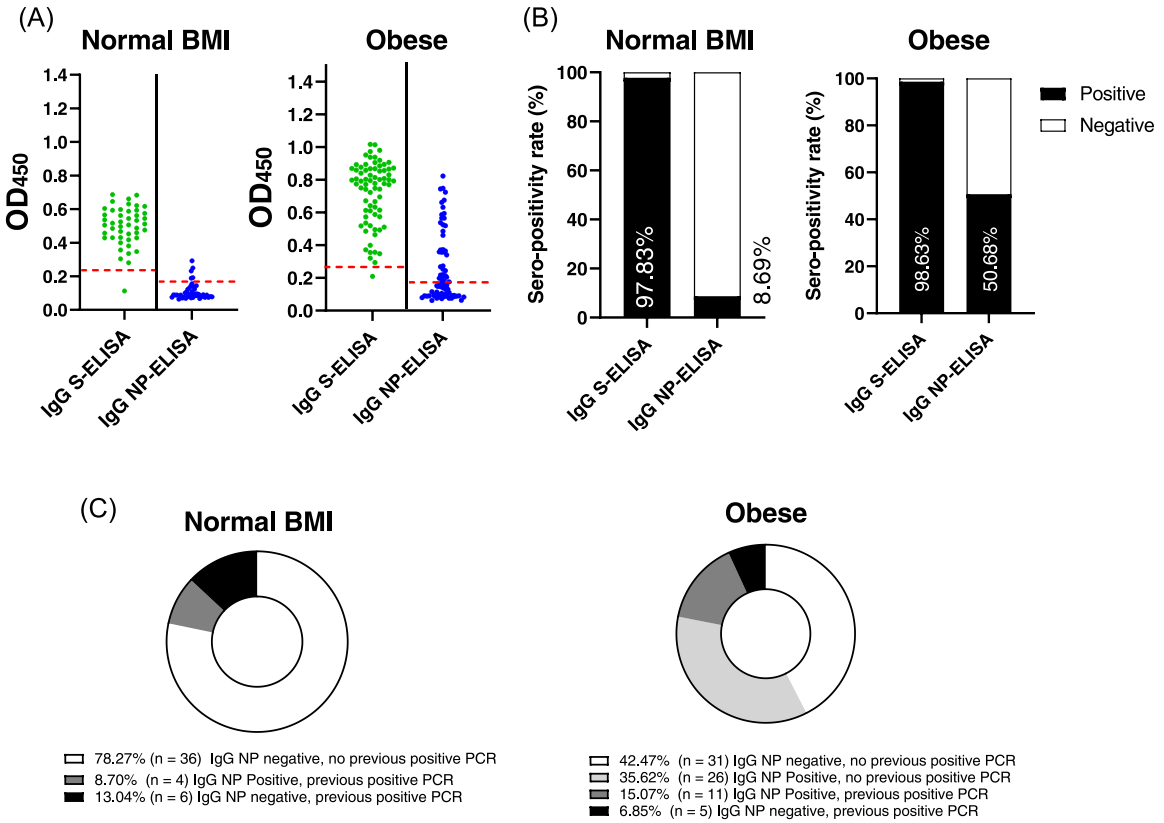

FIGURE 1 The prevalence of COVID-19 IgG to SARS-CoV-2 S and NP antigens among control (BMI between 18 and 25 kg/m^2) and study (obese with BMI ≥ 30 kg/m^2) groups. Data for control (left panel) and study (right panel) are shown. (A) Optical density values at 450 nm (OD450) of samples obtained from S- and NP-based ELISAs. Dashed red lines represent the cut-off values for S-ELISA (OD450 = 0.27) and NP-ELISA (OD450 = 0.17). (B) The sero-positive rates (%) of IgG directed to SARS-CoV-2 S and NP. (C) The prevalence of IgG to SARS-CoV-2 NP among participants relative to their history of past COVID-19 diagnosis. ELISA, enzyme-linked immunosorbent assay; NP, nucleocapsid.

was included. The overall prevalence rate of IgG to NP antigens was 34.45% (41/119). While only 4 samples out of 46 (8.69%) tested positive among the control group, 37 cases out of 73 (50.68%) were positive (OD450 values >0.17) when tested with the NP ELISA (Figure 1A,B). Interestingly, IgG to NP antigen was detected in only 11 out of the 16 (68%) obese individuals who reported their previous diagnosis with RT-PCR. More interestingly, 26 among those who tested positive by both NP- and S-based ELISAs did not report previous diagnosis with COVID-19 by RT-PCR indicating lack of self-awareness about previous infection (Figure 1C). By excluding all samples with positive NP ELISA, the prevalence of anti-S IgG was 97.22% (35/36) and 97.62% (41/42) among the study and control groups, respectively.

Next, SNT was conducted on all samples to identify whether the presence of obesity influences the antibody neutralizing capacity. In the obese cases, there was a significant reduction ($p < 0.01$) in the rate of obese individuals who possess neutralizing antibodies (60/73; 17.81%) (Figure 2). Interestingly, 12 out of the 13 samples tested negative by SNT were found to be positive by S-based ELISA which may indicate the presence of non-neutralizing antibodies. The single sample tested negative by both S-based ELISA and SN belonged to a female participant aged 43 years old with obesity class III (BMI = 46.24 kg/m^2) and rheumatic disorder. She received two doses of Pfizer-BioNTech vaccine and was not diagnosed previously with COVID-19. The sample was collected 263 days after receiving the second dose. The 12 cases that tested negative by SNT belonged to participants from both genders: 5 (41.67%) males and 7 (58.33%) females and all age groups: 1 case (8.33%) was between 18 and 39 years old, 5 cases (41.67%) were between 40 and 59 years old, and 6 cases (50%) were >60 years of age. Some of these cases had other medical conditions besides obesity. For instance, 7/12 (58.33%) had hypertension, 5/12 (41.67%) had diabetes, 1/12 (8.33%) had asthma, or chronic myeloid leukemia.

On the other hand, the control group with normal BMI showed a 100% match between SNT and S-based ELISA. Only a single negative sample by SNT out of the 46 positive samples by S-ELISA was identified which belonged to a male participant aged 21 years old with normal BMI and asthma. He received heterologous COVID-19 vaccination (BNT162b2 and ChAdOx nCov-2019), and the sample was collected 73 days after receiving the second dose. All other samples from control group were tested positive by SNT and ELISA demonstrating 97.83% vaccine effectiveness in inducing neutralizing humoral immune response (Figure 2).

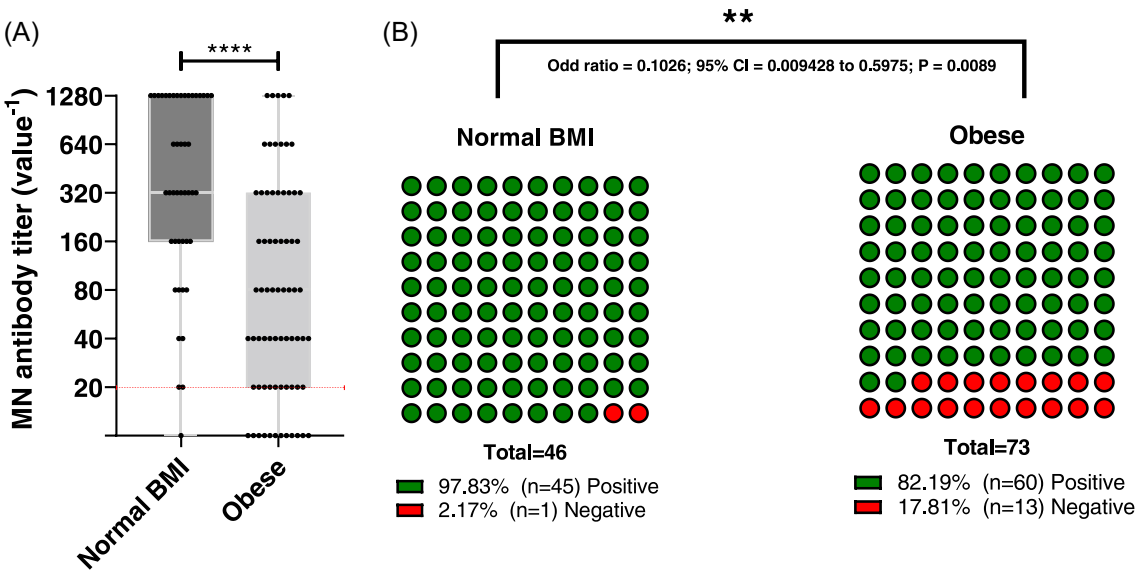

FIGURE 2 The prevalence of COVID-19 neutralizing antibodies among control (normal BMI) and study (obese with BMI ≥ 30 kg/m^2) groups. (A) The anti-SARS-CoV-2 neutralizing antibody titers were determined by serum neutralization assay. Each dot represents the titer of a single sample. Boxes represent minimum to maximum range. Black line represents median. Whiskers show minimum and maximum values. Dashed red lines represent the cut-off values for serum neutralization assay (SN titer of ≥1:20 were considered positive). *p* Values were calculated by Mann–Whitney *U* test. ****$p < 0.0001$. (B) Overall sero-positive rate of anti-SARS-CoV-2 neutralizing antibodies among all samples, and as per control (BMI between 18 and 25 kg/m^2) and study (obese with BMI ≥ 30 kg/m^2) groups. Actual numbers (*n*) and percentages (%), odd ratio, 95% confidence interval (CI), and *p* value is shown as calculated by Fisher's exact test. **$p < 0.01$.

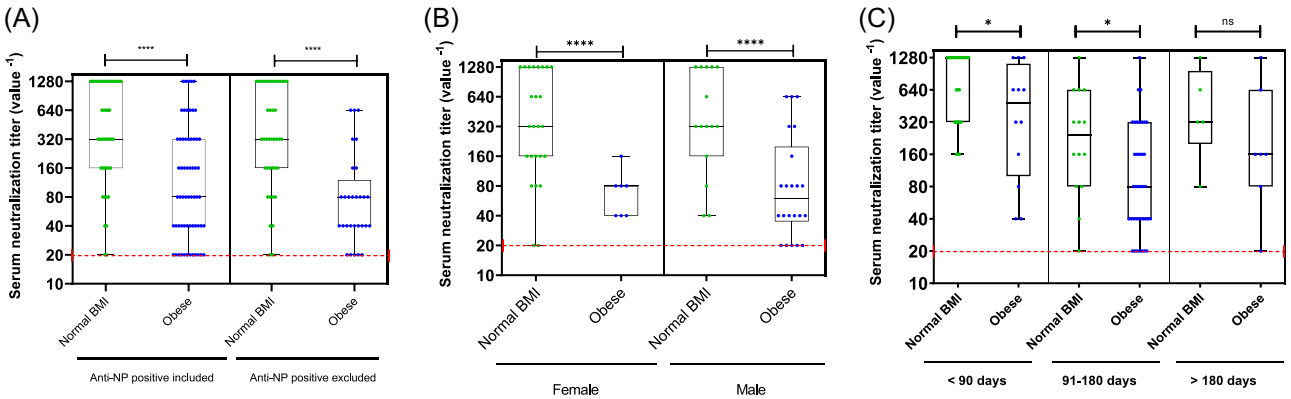

FIGURE 3 Comparison of COVID-19 neutralizing antibody titers among control (normal BMI) and study (obese with BMI ≥ 30 kg/m^2) groups. The anti-SARS-CoV-2 neutralizing antibody titers were determined by serum neutralization assay. Each dot represents the titer of a single sample. (A) Shows data when samples with anti-NP positive was included and excluded. (B) Demonstrates data as per gender. (C) Data was categorized according to the number of days since receiving of last vaccine shot. Boxes represent minimum to maximum range. Black line represents median. Whiskers show minimum and maximum values. Dashed red lines represent the cut-off values for serum neutralization assay (SN titer of ≥1:20 were considered positive). *p* Values were calculated by Mann–Whitney *U* test. *$p < 0.05$, ****$p < 0.0001$, and ns, $p > 0.05$. NP, nucleocapsid.

Further analysis of samples tested positive by SN assay revealed significant reduction ($p < 0.0001$) in SNT titer of obese individuals in comparison to control group. Excluding samples with previous exposure to the infection as indicated by their positive NP ELISA did not change the significance of titer reduction (Figure 3A). The reduction in SNT titer remained significant when the data was analyzed as per gender and period from last vaccination, with exception of those received their last vaccine shot more than 180 days ago (Figure 3B,C).

Next, the effect of several factors including gender, obesity class, age group, type of vaccine, period from last vaccination, and copresence of IgG to the viral S and NP antigens on the SN titers of obese people was investigated (Figure 4). The only factors showing significant effects on the level of neutralizing antibodies was the

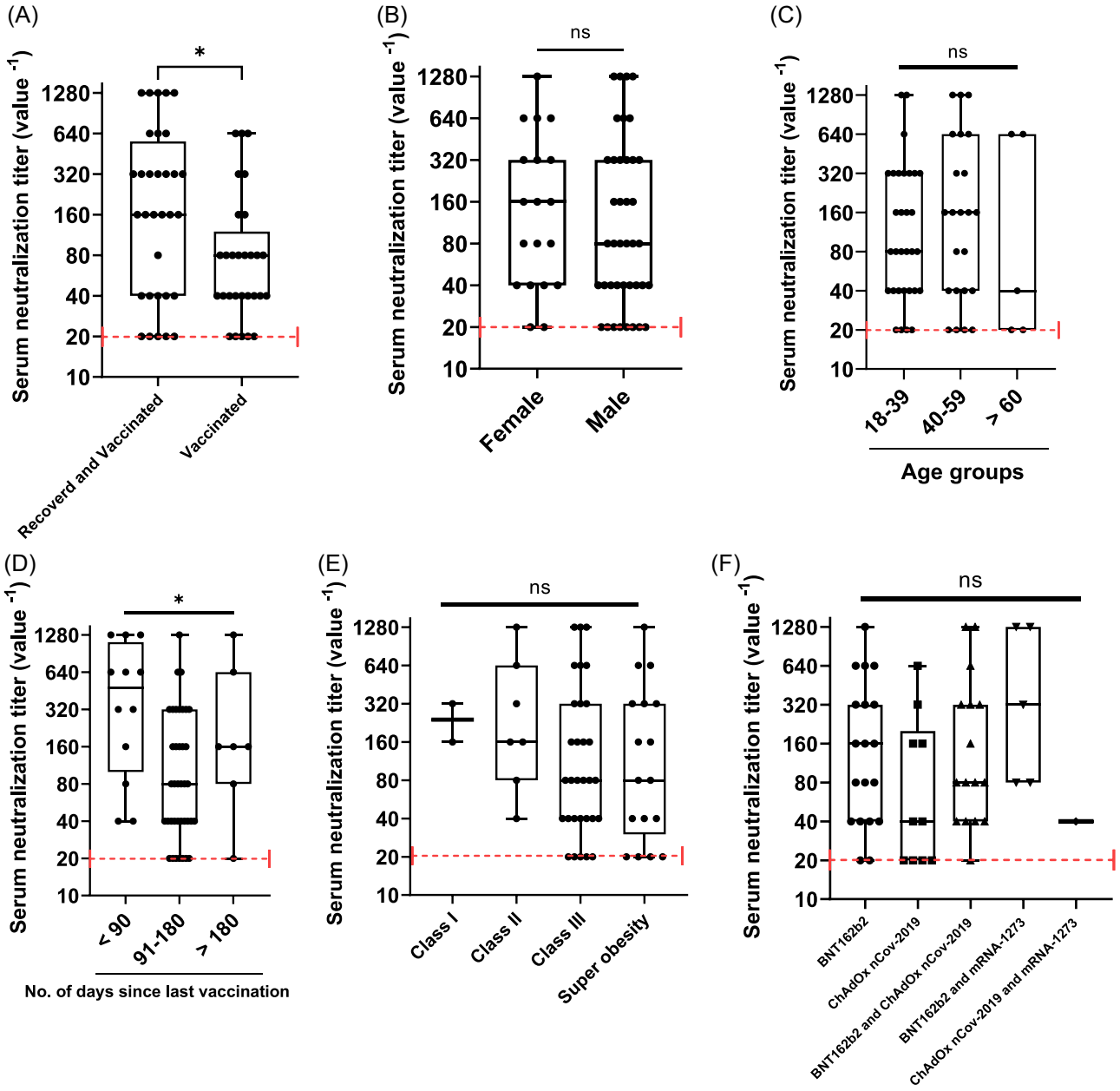

FIGURE 4 The effect of (A) past infection, (B) gender, (C) age, (D) period from last vaccination, (E) obesity class, and (F) type of vaccine on the serum neutralization titer of obese individuals. Boxes represent minimum to maximum range. Black line represents median. Whiskers show minimum and maximum values. Kruskal–Wallis test and Mann–Whitney *U* tests were applied as appropriate with $p \leq 0.05$ considered statistically significant. ns, nonsignificant; $^{**}p < 0.05$.

period from last vaccination or recovery from past infection. Age, gender, class of obesity, and type of vaccination did not have a significant effect on the SNT titer (Figure 4).

4 | DISCUSSION

Obesity is a major health issue worldwide and particularly here in Saudi Arabia as it ranked among the top countries with the highest obesity prevalence rates.[2,3] According to local studies and national reports from the Ministry of Health, overweight and obesity affect more than half of the Saudi population.[32–35] The consumption of high level of saturated fat and refined carbohydrates, and low levels of physical activity have been identified as major risk factors for obesity in Saudi Arabia.[32–35]

Increased vulnerability to various viral infections, and reduced effectiveness of vaccines have been reported among obese individuals.[9,18,20] With the ongoing COVID-19 pandemic, accumulating evidence demonstrated obesity as a risk factor to aggravates the outcome of SARS-CoV-2 infection.[9,11,12,14,19,20] The underlying mechanisms are not fully clear, but impaired immunity, decreased lung capacity, and preexisting inflammatory status are likely involved

in this matter. With the availability of COVID-19 vaccines, a number of studies highlighted the importance of prioritizing individuals with obesity.[11,19] Acknowledging the effect of obesity on host immunity, it is crucial to determine the effectiveness of COVID-19 vaccines on the induction of neutralizing immunity in obese people. This is particularly vital taking into consideration the studies suggesting reduction in some vaccine effectiveness (e.g., influenza virus and hepatitis B vaccines) among obese individuals in addition to the emergence of reports about the vaccine-breakthrough SARS-CoV-2 infections among obese individuals.[11,20,22,23]

In this study, we targeted individuals of different age groups (18–39, 40–59, and ≥60) from both genders (male and female) with various degree of obesity (class I with BMI range of 30–34.99 kg/m,^{2} class II with BMI range of 35–39.99 kg/m,^{2} class III with BMI range between 40 and 49.99 kg/m,^{2} and super obesity with BMI ≥ 50 kg/m^2). Control group with normal BMI were included in the study to validate the conclusions about the vaccine effectiveness among obese individuals. All participant recruited in this study and control groups received two doses of either homologous or heterologous COVID-19 vaccines that are currently approved for use in Saudi Arabia (BNT162b2 by Pfizer-BioNTech, ChAdOx nCov-2019 by AstraZeneca, or mRNA-1273 by Moderna). All three vaccines aim to generate neutralizing immunity to the viral S protein; a key protein for viral attachment to target cells. All samples were initially subjected to our lab-developed S-based ELISA that enables detection of human IgG antibodies against the viral S protein. Results demonstrated high prevalence rate in both study (obese) and control groups (98.63% and 97.83%, respectively). No statistically significant difference in vaccine effectiveness was found. Interestingly, however, the neutralizing capacity of antibodies generated by the obese individuals demonstrated significant reduction compared to control group. Indeed, the prevalence of neutralizing antibodies was significantly lower (82.19%) among obese individuals compared to the control group (97.83%). Further, investigations on those tested positive by SNT assay revealed significant reduction on SNT titer among obese individuals in comparison to the control group. This finding was true for both genders and whether past infected cases were included or excluded. Similar findings were observed among those who received their last vaccination in less than 90 days or between 91 and 180 days. Samples obtained from obese individuals and tested positive by SNT assay revealed no significant effect of class of obesity, gender, age group, or type of vaccine received on the SN titer. On the other hand, those who had evidence of past infection (positive NP-ELISA) among the study group had significantly higher SNT titer in comparison with their corresponding controls to those who acquired immunity though vaccination only (negative NP-ELISA). Similarly, those who received their last vaccine shot within 90 days had significantly higher SN titer compared to other groups (91–180 and >180 days).

Our study, similar to previous reports, demonstrated high effectiveness of COVID-19 vaccines in inducing humoral immunity.[24–28] However, there is a significant reduction in vaccine effectiveness in inducing neutralizing antibodies among obese individuals. Whether this reduction is due failure to mount neutralizing immune response or higher waning rate of humoral immune response remain vague. Regardless, these findings may explain the accumulating reports describing vaccine-breakthrough SARS-CoV-2 infections among obese individuals.[20] The negative impact of obesity on host immunity is not unique to COVID-19, as it has been repeatedly reported with other microbial infections and vaccinations. For instance, obesity is associated with increased risk of tetanus, influenza, and hepatitis B vaccine failure.[18,22,23] The underlying mechanisms are not fully understood. Alteration of lymphoid tissue integrity, impaired coordination between innate and adaptive immunity, decreased activity of antigen presenting cells, and failure to maintain pathogen-specific memory cells under obesity settings have been described.[20,36] In this study, the reasons for reduced effectiveness of COVID-19 vaccines in obese individuals is unknown and require further investigations. However, the current data obtained from ELISA and SNT highlights the importance of considering neutralization assay to comprehensively conclude about the vaccine effectiveness. This is particularly important as most previous studies assessed COVID-19 vaccine effectiveness utilized immunoassays that can detect anti-SARS-CoV-2 antibodies but lack the ability to determine their neutralization capacity.[24–28] It is also vital to note that SNT in many instances, as in our study, is conducted solely against a single SARS-CoV-2 isolate, and the level of protective immunity may vary with other SARS-CoV-2 variants. Our study is also limited by the relatively small number of samples considering the large heterogenicity of the study subject. Several factors such as age, gender, vaccination profile, previous COVID-19 positivity could act as major confounding factors, limiting significantly the obtained results. As an effort to overcome this issue, we have further subdivided our study population into subgroups and analyzed the data based on their gender, previous COVID-19 positivity, vaccination profile, and obesity class. Although our results sustained the same conclusion with regard to obesity-associated reduction of COVID-19 vaccine effectiveness, we would like to emphasize that evaluation a more homogeneous study group and/or substantial increase in the number of samples remain necessary to comprehensively conclude about the effect of obesity on COVID-19 vaccine effectiveness on humoral immunity induction.

One of the key findings noted in this study was the number of cases who were unaware of previous exposure to SARS-CoV-2 infection. Indeed, 26 obese individuals and 1 control participant (normal BMI) demonstrated evidence of previous infection (NP-positive ELISA) but they did not report their past infection. Since the pandemic started, many studies reported asymptomatic cases with lack of self-awareness which probably increased due to the emergence of variants with high transmissibility and mild pathogenicity (e.g., Omicron; B.1.1.529).[31,37–40] We also found 11 recovered cases (6 with normal BMI and 5 with various degree of obesity) with confirmed PCR diagnosis tested negative for IgG NP-ELISA which supports previous studies that reported antibody waning following recovery.[37,41,42] These results demonstrate the potential vulnerability

of recovered patients to reinfection and highlight the importance of vaccination uptake for this population.

5 | CONCLUSIONS

COVID-19 and obesity are interconnected global pandemic. Severe COVID-19 symptoms among obese individuals highlighted the importance of prioritizing them to receive the vaccination. Herein, we provided preliminary evidence of reduced effectiveness of COVID-19 vaccines in inducing neutralizing humoral immunity among individuals with various classes of obesity compared to control with normal BMI. These data highlight the importance of obtaining the booster dose as recommended by several health authorities. A key finding of this study was the necessity of assessing the neutralizing capacity, not only the presence, of anti-SARS-CoV-2 antibodies to properly evaluate the vaccine effectiveness. Similar studies on larger size of study population, and investigations on vaccine-induced cell-mediated immunity are required to comprehensively conclude about the effect of obesity on COVID-19 vaccine effectiveness.

AUTHOR CONTRIBUTIONS

Conceptualization: Arwa A. Faizo, Fadi S. Qashqari, Osamah Barasheed, Mohammed Alfelali, and Thamir A. Alandijany. *Methodology*: Arwa A. Faizo, Fadi S. Qashqari, Majed N. Almashjary, Asma A. Bawazir, Boshra M. Albarakati, Soud A. Khayyat, Ahmed M. Hassan, and Thamir A. Alandijany. *Software*, Arwa A. Faizo and Thamir A. Alandijany. *Validation*: Arwa A. Faizo, Sherif A. El-Kafrawy, Thamir A. Alandijany, and Esam I. Azhar. *Formal analysis*: Arwa A. Faizo, Sherif A. El-Kafrawy, Thamir A. Alandijany, and Esam I. Azhar. *Investigation*: Fadi S. Qashqari, Asma A. Bawazir, Ahmed M. Hassan, and Boshra M. Albarakati. *Resources*: Fadi S. Qashqari, Osamah Barasheed, Majed N. Almashjary, Thamir A. Alandijany, and Esam I. Azhar. *Data curation*: Arwa A. Faizo, Fadi S. Qashqari, and Thamir A. Alandijany. *Writing – original draft preparation*: Arwa A. Faizo, Sherif A. El-Kafrawy, and Thamir A. Alandijany. *Writing – review and editing*: all authors. *Visualization*: Thamir A. Alandijany. *Supervision*: Arwa A. Faizo, Thamir A. Alandijany, and Esam I. Azhar. *Project administration*: Thamir A. Alandijany and Esam I. Azhar. *Funding acquisition*: Thamir A. Alandijany. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Biomedical Research Ethics Committee of Umm Al Qura University (protocol code HAPO-02-K-012-2021-09-747 and date of approval 7/9/2021) and the Institutional Review Board of King Abdullah Medical City (protocol code 21-779 and date of approval 1/7/2021). Informed consent was obtained from all subjects involved in the study.

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