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Antibody-dependent enhancement of SARS-CoV-2, the impact of variants and vaccination

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ABSTRACT

This study characterized antibody-dependent enhancement (ADE) in serum samples from individuals exposed to SARS-CoV-2 via infection or vaccination and evaluated its association with SARS-CoV-2 variants (Wuhan and Omicron), MERS-CoV, and NL63. ADE assays were performed on sera from SARS-CoV-2-infected patients ($n = 210$) with varying disease severity and vaccinated individuals ($n = 225$) who received adenovirus vector, inactivated virus or mRNA vaccines. ADE was assessed using pseudoviruses (PVs) in BHK cells expressing FcgRIIa. Neutralizing antibody levels, total IgG, IgG subclasses, and complement activation were analyzed using ELISA and neutralization assays. ADE was observed in 6.2% of infection samples (primarily severe cases) and 5.3% of vaccinated samples (adenovirus-vector and inactivated virus groups). ADE-positive samples showed reduced neutralizing activity, while total IgG and IgG subclasses did not differ significantly between ADE-positive and negative samples. Complement activation was elevated in severe cases but did not correlate clearly with ADE. Notably, MERS-CoV PV induced ADE in a subset of infected samples, but no ADE was detected for NL63. ADE was observed in SARS-CoV-2-infected individuals, particularly in severe cases, and in those vaccinated with adenovirus-vector and inactivated virus vaccines, but not with mRNA vaccines. Cross-reactivity leading to ADE was detected for MERS-CoV but not for NL63. ADE was associated with reduced neutralizing antibody activity and elevated complement activation in severe infections, though the specific role of complement in ADE remains unclear. These findings highlight the need to investigate the mechanisms underlying ADE and its implications for vaccine design and post-infection immunity against respiratory viruses.

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Virology; SARS-CoV2; ADE; immunology; variants

Introduction

Antibody-dependent enhancement (ADE) has become a notable concern during the COVID-19 pandemic, especially with the emergence of SARS-CoV-2 variants. ADE occurs when suboptimal or non-neutralizing antibodies – arising from previous infection or vaccination – enhance viral entry into host cells via Fc gamma receptors (FcgR) or complement receptors (CR), potentially worsening disease severity. This phenomenon has been demonstrated both in vitro and in vivo for coronaviruses such as SARS-CoV and MERS-CoV.[1] For instance, Macaques immunized against MERS-CoV showed a higher load of viral RNA in the lungs and higher lung pathology when compared to immunosuppressed Macaques.[2] Similarly, live SARS-CoV strain in human immune cells (THP-1, Raji B cells) was reported in 2011 in the presence of mouse-derived anti-spike antibodies,[3] and ADE of monocyte-derived macrophages was shown to involve IgG-FcgRIIa-mediated mechanism.[4] In dengue infection, non-neutralizing IgGs with enhanced affinity for FcgRIIIa were strongly correlated with disease pathology and ADE.[5,6] For SARS-CoV, ADE was reported when pseudoviruses (PVs) were exposed to diluted spike-specific antibodies from infected individuals,[7] and recent studies have also identified evidence of ADE in patient's serum with SARS-CoV-2 infection.[1,8] Another study has also identified evidence of ADE during SARS-CoV-2 infection, where infectivity-enhancing antibodies co-exist alongside neutralizing antibodies.[9] *In vitro* findings also reported FcgR-mediated ADE of SARS-CoV-2 PVs in the presence of convalescent plasma from severe COVID-19 patients.[10–12] Other studies observed FcgR/or C1q (complement1q) mediated ADE in almost 50% (out of 89) of serum samples from patients with severe COVID-19 infection,[13] and FcgRIIa mediated ADE of SARS-CoV-2 PVs in serum samples from severely infected patients.[10] The study investigated FcgRIIa-mediated antibody-dependent enhancement (ADE) of SARS-CoV-2 PVs in serum samples from patients with severe infections. It demonstrated that PV entry into BHK cells expressing FcgRIIa was enhanced, highlighting a possible mechanism of ADE. These findings suggest that ADE-inducing antibodies might play a role in exacerbating disease severity in COVID-19 cases.

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Vaccine-associated ADE (VADE) has also been actively investigated during the COVID-19 vaccine development and rollout. Previously, VADE has been reported to have respiratory viral infections after vaccination for measles,[14,15] influenza,[16] and respiratory syncytial infection (RSV).[17] After measles vaccination, IgG-mediated ADE was observed in mouse and human macrophages, where preexisting antibody-virus complexes inhibited B cell activation, leading to enhanced infection.[14] Similarly, measles-specific IgG in cotton rats inhibited seroconversion via cross-linking between FcgRIIb and the B cell receptor.[15] In influenza, sub-neutralizing monoclonal antibodies demonstrated cross-reactive ADE across three viral strains, whereas strain-specific antibodies effectively neutralized infection.[16] One of the most notable cases of VADE occurred in the 1960s when formalin-inactivated RSV (FI-RSV) vaccination in children led to enhanced respiratory disease (ERD), a broader form of ADE characterized by severe immunopathology following natural RSV infection.[18]

Vaccine-associated disease enhancement (VADE) has also been observed in studies involving SARS-CoV and MERS-CoV. In the case of SARS-CoV, inactivated virus vaccines containing the spike (S) protein led to increased lung pathology in mice following viral challenge.[19] Similarly, a full-length MERS-CoV spike (S) protein-based vaccine failed to protect against infection in animal models. Instead, it induced non-neutralizing antibody responses, heightened inflammatory reactions, and aggravated hepatitis.[20] Notably, suboptimal concentrations of neutralizing monoclonal antibodies against SARS-CoV-2 S protein enhanced infection of SARS-CoV-2 PV in FcgRIIb-expressing B cells.[21] Furthermore, a sequence comparison of complementarity-determining regions (CDRs) identified significantly higher levels of ADE-inducing antibodies in SARS-CoV-2-infected and vaccinated individuals compared to unexposed healthy donors.[22]

The widely proposed mechanism of ADE in respiratory viral infections involves the deposition of virus-immune complex and cytokines in the airway sacks, which triggers complement activation and cytokine release.[1,23] This cascade leads to upregulation in inflammation, obstruction in the airway, and acute distress respiratory syndrome (ADRS), exacerbating disease severity.[17] Evidence also suggests that ADE is closely associated with IgG levels rather than IgA or IgM.[24] Clinical observation reports have shown similarities between severe SARS-CoV-2 and RSV infections, particularly concerning hyperactivation of complement cascade and lung inflammation.[25] Elevated complement activation, specifically in severe COVID-19 cases, further highlights its contribution to disease pathogenesis.[25,26] A comprehensive understanding of the underlying mechanisms of antibody-dependent enhancement (ADE) in SARS-CoV-2 severe infection and vaccination is critical for advancing the development of safe and effective therapeutics and vaccines. By elucidating these processes, this study aims to contribute to the refinement of immunization strategies and the mitigation of potential risks associated with ADE, ultimately enhancing global efforts to control and prevent severe COVID-19 outcomes.

Methods

Patients and samples

In this study, we analyzed a total of 455 serum samples collected from 216 individuals exposed to coronaviruses through either SARS-CoV-2 infection ($n = 210$) or vaccination ($n = 225$), as detailed in Table 1. Serum samples from patients in the infected groups were collected within 21 of hospital admission, while samples from the vaccinated group were obtained between two weeks to four months following vaccination. The sample size for the SARS-CoV-2 infection group was determined based on previous research findings.[10] Additionally, 25 age- and gender-matched pre-pandemic control samples were randomly selected for comparative analysis.

Generation and titration of pseudoviruses

Pseudoviruses (PVs) expressing the spike (S) proteins of wild-type SARS-CoV-2 the Omicron variant, MERS-CoV, and NL63 were generated in HEK293T cells (human embryonic kidney cells) using recombinant ΔG-Vesicular Stomatitis Virus (VSV ΔG) vectors carrying a luciferase reporter, as previously described.[27] The PVs were titrated in HEK293T cells expressing either ACE2 (for SARS-CoV-2 and NL63) or DPP4 (for MERS-CoV) receptors, following established protocols.[28] Viral titers were quantified by measuring luminescence using a TECAN Infinite F200 PRO plate reader, reported as relative luminescence units (RLU) per well and then converted to RLU/ml.

Table 1. Demographic and clinical information of samples in this study.

	# of samples	Sample Time points	# of patients	Gender (Male)	Median age
SARS-CoV-2 Infected					
ICU	75	TP-1 (1–7 DPI) TP-2 (8–14 DPI) TP-3 (15–21 DPI)	25	25(100 %)	68.5
Severe Non-ICU	70	TP-1(1–7 DPI) TP-2 (8–14 DPI)	35	31(88.5 %)	45
Mild infected	65	TP-1(1–7 DPI)	65	44(67.7%)	39
Total infected	**210**		**125**		
SARS-CoV-2 Vaccinated		Doses			
Adenovirus vector (Ad-vector) vaccine	75	3 doses	25	9 (36%)	50
Inactivated virus vaccine	75	3 doses	25	NA	NA
mRNA vaccine	75	3 doses	25	11 (44%)	49
Total vaccinated	**225**		**75**		
Total	**435**		**200**		

ADE assays

To evaluate ADE, we employed baby hamster kidney (BHK) cells stably expressing the human Fc gamma receptor IIa (FcgRIIa), generously provided by Yoshihiro Kawaoka et al.[10] Stable expression of FcgRIIa was confirmed via immunofluorescence assay.[29] ADE assays were carried out using PVs bearing spike proteins of SARS-CoV-2 (Wuhan and Omicron variants), MERS-CoV, or NL63, following previously established protocols with minor modifications.[30] Prior to the assay, serum samples were heat-inactivated at 56°C for 30 minutes and serially diluted (1:6 to 1:60,000) in high-glucose DMEM without fetal bovine serum (FBS). For each sample, 50 µl of diluted serum (six serial dilutions) was incubated with 50 µl of PVs (1×10^6 RLU/ml) at 37°C for 30 minutes. After incubation 50,000 BHK-FcgRIIa cells in 100 µl of DMEM without FBS were added to each well, and the immune complexes were co-incubated with the cells for an additional 60 minutes at 37°C.Following this, the medium was replaced with 200 µl of DMEM supplemented with 10% FBS, and the cells were incubated for 48 hours at 37°C. Post-incubation, cells were washed with 1 × PBS, lysed using 50 µl of lysis buffer (Bio-Glo™ Luciferase Assay System, Promega, USA) for 20 minutes, and subsequently treated with 50 µl of luciferase substrate. Luminescence was measured using a TECAN Infinite F200 PRO plate reader. ADE was quantified by comparing the luminescence signal of serum-treated wells to that of control wells.

Neutralization assays

The neutralizing antibody levels in serum samples were analyzed using PVs of SARS-CoV-2 (Wuhan and Omicron), MERS-CoV, or NL63. HEK293T cells expressing the ACE-2 receptor and Huh7.5 cells expressing the DPP4 receptor were used to assess the percentage inhibition (viral entry) of SARS-CoV-2 and MERS-CoV PVs, respectively. Heat-inactivated serum samples were serially diluted into six two-fold serial dilutions (in duplicates) starting from 1:50 to perform neutralization assays as previously described.[31] The luminescence was measured with a TECAN infinite F200 PRO plate reader. The percentage neutralization was calculated for each sample dilution against the luminescence of non-serum controls (PV concentration = 1×10^6 RLU/ml).

ELISA to detect serum IgG subtypes

ADE-positive and negative samples were analyzed for the level of total IgG and subtypes against SARS-CoV-2 S1 and RBD proteins, including IgG1, IgG2, IgG3, and IgG4, using sandwich ELISA as described elsewhere[32] with necessary modifications. We evaluated the titer of total IgG and subtypes in all ADE positive samples at all timepoints from SARS-CoV-2 infected and vaccinated groups. Briefly 96 well plate was coated with 50 µl of SARS-CoV-2 'S' protein/well to a final concentration of 1 µg/ml. The plate was covered and incubated overnight at 4°C. After incubation, the coating buffer was completely discarded. Serum samples were diluted to 1:50 using blocking buffer (1 % BSA in 1X PBS), and each sample was analyzed separately in duplicates for total IgG and subtypes. The covered plate was incubated for 1 hour and washed four times with 20 µl 1X PBS. Subsequently, 100 µl secondary antibody (1:3000) for total IgG and subtypes (Invitrogen, USA) was added separately to the wells and incubated for 1 hour at room temperature. After incubation, the plate was washed 3 times with 1X PBS, and 100 µl substrate was dispensed into each well and incubated for 5 minutes in the dark before adding the stop solution. Absorbance at 450 nm was measured, and graphs were generated to display total IgG levels and the percentage of each IgG subtype against four subgroups across three groups: ADE-positive, ADE-negative, and pre-pandemic control samples, for each target protein.

ELISA to detect serum complement levels

Serum samples were screened for the level of complements including, C1q, C3, C3a, and C5a using ELISA kits, Invitrogen; BMS2099(C1q), EHAPOC3(C3), BMS2089(C3a) and MBS2088(C5a), as per manufacturer's protocol. In brief, samples and standards were diluted and incubated in anti- human complement coated 96-well plate. After 2 hours of incubation at room temperature, biotin-conjugated anti-human C5a is added to the plates and incubated for 1 hour at room temperature. Subsequently, streptavidin-HRP was added to each well and incubated for 1 hour at room temperature before adding TMB substrate. After 20 incubation with the substrate, the enzyme reaction was stopped using the stop solution. Absorbance was measured at 450 nm and a reference wavelength of 650 nm with a BioTek citation 5 plate reader.

Statistical analysis

All statistical analyses were performed in GraphPad Prism 9. One-way ANOVA was used to analyze the differences between groups of complements assay (Bartlett's test), unpaired t-test for ADE assay, and ordinary one-way ANOVA (One sample t and Wilcoxon test) for neutralization assay. Ordinary one-way ANOVA (Bartlett 's-Forsythe test) was used to analyze the total IgG and IgG subclass test results. The p-value less than 0.05 was considered statistically significant.

Results

Patients and samples

In this study, we characterized the ADE of SARS-CoV-2 (Wuhan and Omicron), MERS-CoV, and NL63 in serum samples from SARS-CoV-2-infected and/or vaccinated individuals. We analyzed the association of antibody neutralization activity with ADE. We also evaluated the level of total IgG, IgG subtypes, and serum complements and their association with ADE.

SARS -CoV-2 infection samples

The SARS-CoV-2 infection samples ($n = 210$) were collected from 125 adult SARS-CoV-2 infected patients with different disease severity (Table 1). Serum samples were from 25 ICU admitted patients (three different time points; TP-1, TP-2, and TP-3 ($n = 75$)), 35 severe non-ICU patients (two different time points; TP-1 and TP-2 ($n = 70$)) and 65 mild infected patients

(one-time point; TP-1(n = 65)). The age of ICU patients ranged between 44 and 91(median age = 68.5), severe non-ICU patients ranged between 25 and 65 (median age = 45), and mild infected patients ranged between 13 and 65 (median age = 39). All ICU and severe non-ICU patients were male; however, among mildly infected patients, 42 were males, and n = 23 were females.

SARS -CoV-2 vaccination samples

A total of 225 serum samples were collected from 75 individuals who received different doses of three types of SARS-CoV -2 vaccines: adenoviral vector (AstraZeneca,ChAdOx1-nCoV -19), inactivated virus (Sinopharm, BBIBP-CorV), and mRNA-based (Pfizer,BNT162b2) vaccines (Table 1). For both the Ad-vector and mRNA vaccines, serial samples were collected from 25 individuals three timepoints – following the 1st, 2nd, and 3rd doses. In contrast, for the inactivated virus vaccine group, serial sampling was not available; instead, samples were collected from different individuals who had received one, two, or three doses. Participants vaccinated with the Ad-vector vaccine ranged in age from 36 to 64 years (median age: 50), with females comprising 64% (16 out of 25) of this group. Those who received the mRNA vaccine were between 32 and 66 years old (median age: 49), and the gender distribution was 56% male (14 out of 25) and 44% female (11 out of 25). Demographic information for individuals who received the inactivated virus vaccine was not available for analysis.

Assessment of ADE activity in serum samples exposed to coronaviruses

ADE was characterized as the entry of PVs into BHK cells expressing FcgRIIa, but not ACE-2, in the presence of anti-SARS-CoV-2 serum samples. We evaluated ADE using serum samples from individuals with varying degrees of SARS-CoV-2 infection severity, as well as from individuals who received different doses of the SARS-CoV-2 vaccine. ADE activity was quantified by measuring the relative luminescence units (RLU) of each sample, comparing the results to control samples from pre-pandemic serum from healthy individuals.

ADE of SARS-CoV-2 in serum samples with SARS-CoV-2 infection

We first tested whether serum from SARS-CoV-2 infected patients mediates ADE activity of SARS-CoV-2 PV in FcgRIIaa expressing BHK cells. We observed higher luminescence (assessed at 24 dpi) in 13 serum samples from SARS-CoV-2 severe patients compared to pre-pandemic samples. Higher luminescence indicating enhanced PV entry (ADE) was observed at higher serum dilutions of 1:3200 and declined in following dilutions. Of the total serum samples tested, 13 samples (out of 210) demonstrated ADE activity. Interestingly, all the 13 ADE-positive samples were from severe infected patients; contributing to 8.9% of severe infection samples (n = 145; ICU (n = 75) and severe non-ICU (n = 70)). Expectedly, none of the serum samples from mild infected patients (n = 65) demonstrated higher luminescence activity, indicating no ADE in anti-sera from SARS-CoV-2 mild infection (Figure 1 and Table 2). Further, our analysis revealed that of the 13 ADE-positive samples, 12 samples are from four ICU-admitted patients collected at three different time points (TP-1(1–7 DPI), TP-2 (8–14 DPI), and TP-3 (15–21 DPI)). However, only one sample from severe non-ICU patients (n = 75) showed a significantly higher level of luminescence when compared to the pre-pandemic control samples.

ADE of SARS CoV-2 in serum samples with SARS-CoV-2 vaccination

Further, we characterized ADE of SARS-CoV-2 PV in serum samples from SARS-CoV-2 vaccinated individuals. We compared ADE in samples from individuals who had been administrated one dose (n-25), two doses (n = 25), and three doses (n = 25) each for Ad-vector, inactivated virus, and mRNA vaccines. Significant ADE, indicated by higher luminescence signals, was observed in 12 (out of 225) of SARS-CoV-2 vaccination samples. Further analysis revealed that out of 12 ADE-positive samples, seven were Ad-vector vaccination, and five were inactivated virus vaccination. However, none of the mRNA vaccination samples showed higher luminescence than pre-pandemic control samples, indicating no ADE in serum samples from mRNA vaccination. Among Ad- vector ADE-positive samples (9.3 %; 7 of 75), one participant showed ADE in serum samples after the 1st, 2nd, and 3rd dose (all samples were serial samples from 25 individuals). The second participant showed ADE in the 1st and 2nd dose samples only, while two other participants showed ADE only in the 3rd dose samples. Of five ADE-positive samples with inactivated virus vaccine (not serial samples), samples were from one dose (one sample), two doses (two samples), and three doses (two samples) of vaccine administration (Figure 2 and Table 2).

Assessment of ADE of SARS-CoV-2 Omicron, MERS-CoV and hCoV

We then characterized ADE of SARS-CoV-2 variant Omicron, MERS-CoV, and hCoV (NL63) in ADE-positive and randomly selected ADE-negative samples from previous ADE assays (SARS-CoV-2 Wuhan PV). Results of ADE assays with PVs generated from S protein of SARS-CoV-2 Omicron, MERS-CoV, and NL63 revealed that all 13 ADE-positive samples from SARS-CoV-2 infection group PV showed similar levels of ADE when treated with SARS-CoV-2 Omicron PV (p-value = .0015). However, only three out of 12 ADE-positive samples from the SARS-CoV-2 vaccination group demonstrated higher luminescence when treated with SARS-CoV-2 Omicron PV (p value = 0.0428). Interestingly, along with the majority of ADE-positive samples from the previous ADE assay, three more samples (ADE-negative in the previous ADE assay) demonstrated ADE when treated with MERS-CoV PV (p-value = .0164). Further, we also evaluated ADE of NL-63 PV in samples positive for ADE of SARS-CoV-2 Wuhan strain from SARS-CoV-2 infected and vaccinated cohorts. Still, none of the samples showed significantly higher luminescence when treated with NL-63 PV, indicating no ADE (Figure 3).

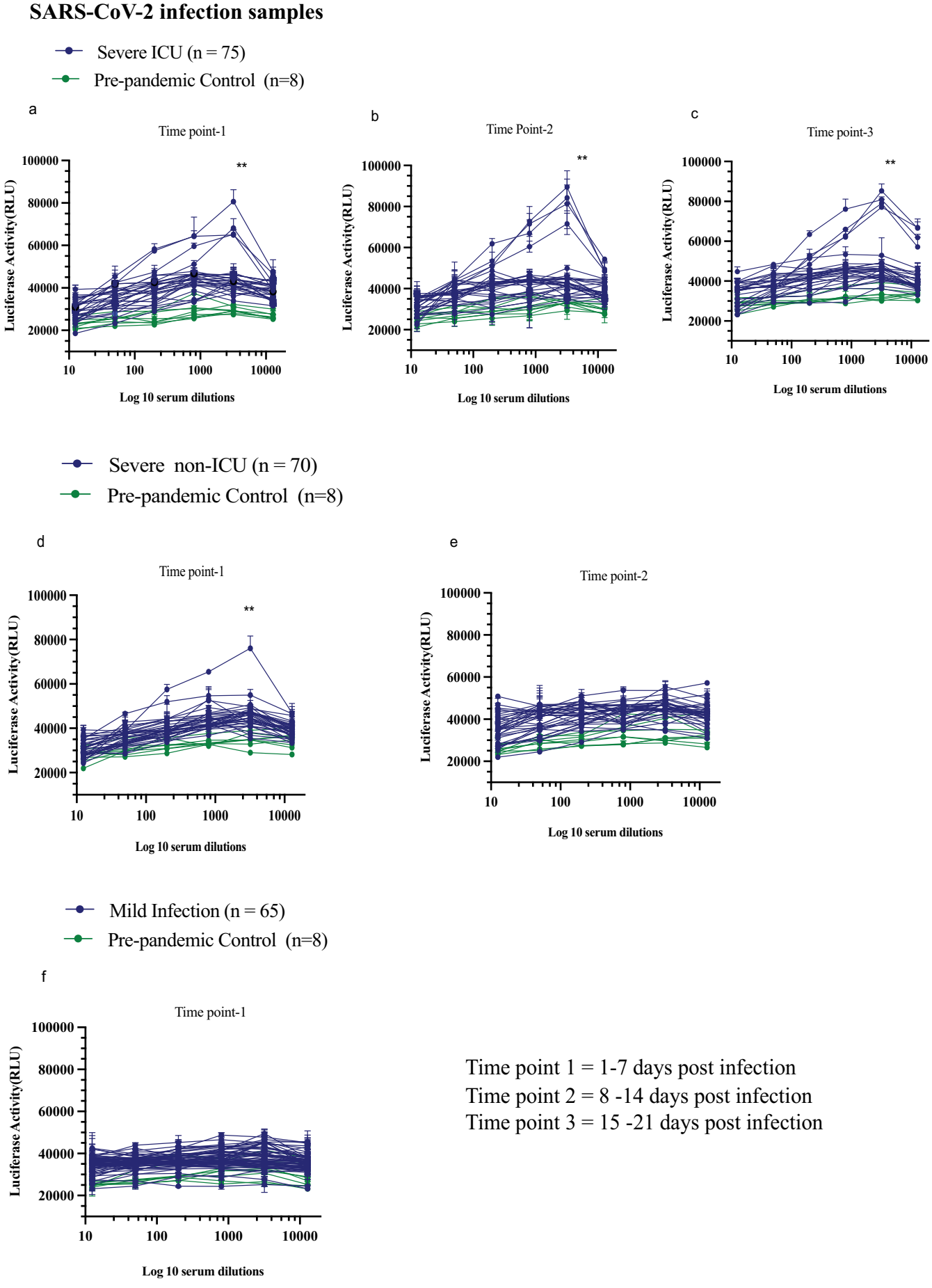

Figure 1. ADE of SARS-CoV-2 in COVID-19 infected serum samples; ADE in samples from ICU patients; TP1 (a), TP2 (b), and TP3 (c); severe non-ICU patients; TP1 (d), TP2 (e); mild infection; TP1 (f). ADE is indicated as significantly higher luminescence signals between serum dilutions of SARS-CoV-2 infected and control samples. Statistical analysis was performed using unpaired t test and the significance is indicated by **(*p* value 0.0022, <0.0001, 0.0312, 0.0247).

Table 2. ADE positive samples in SARS-CoV-2 in SARS-CoV-2 infection and vaccination.

Patient/Sample ID	Gender	Age at the time of sample collection (years)	ADE – Time point
SARS-CoV-2-2 infection ICU			
C008	M	60	TP 1,2 and 3
C076	M	65	TP 1,2 and 3
C081	M	66	TP 1,2 and 3
C084	M	50	TP 1,2 and 3
SARS-CoV-2-2 infection Severe non-ICU			
P12 V1	M	60	TP 1
SARS-CoV-2 vaccination (Ad- vector vaccine)			ADE- Dose
AdV007	F	61	Dose 1,2 and 3
AdV018	F	36	Dose 1 and 2
AdV064	F	48	Dose 3
AdV071	M	59	Dose 3
SARS-CoV-2 vaccination (inactivated vaccine)			
IMV003	NA	NA	Dose 1
IMV027	NA	NA	Dose 2
IMV032	NA	NA	Dose 2
IMV045	NA	NA	Dose 3
IMV070	NA	NA	Dose 3

Association of ADE with IgG subtypes and neutralization

Total IgG and IgG subtypes (IgG1 to IgG4) were quantified in both ADE-positive and ADE-negative samples using ELISA. This analysis included 13 ADE-positive samples from four ICU patients (collected across three timepoints), one severe non-ICU patient (one timepoint), and 12 ADE-positive samples from vaccinated individuals across three different vaccine doses. All selected samples, from both SARS-CoV-2 infected and vaccinated groups, were also evaluated for the presence of neutralizing antibodies. Statistical analysis using one-way ANOVA did not reveal any significant differences in the levels of total IgG against SARS-CoV-2 S1 and RBD protein (Supplementary figure 1). Comparison of IgG subtypes between ADE-positive and ADE-negative samples revealed a significantly higher titer of IgG1 and lower titer of IgG4 in ADE-positive samples against S1 protein ($p = .0074$). Additionally, there was a trend toward lower titers of IgG2 and IgG4 against both S1 and RBD proteins, although these differences were not statistically significant (Figure 4).

Neutralization assays were conducted using PVs expressing the spike (S) proteins of SARS-CoV-2 Wuhan, Omicron, and hCoV NL63. ADE-positive samples demonstrated significantly reduced neutralizing activity against Wuhan ($p = .0210$; $R^2 = 0.5635$) and Omicron ($p = .0182$; $R^2 = 0.6218$) PVs compared to ADE-negative samples. However, no significant difference was observed with NL63 PV (Figure 4). Furthermore, within both ADE-positive and ADE-negative groups, there was no significant difference in neutralization activity when comparing samples from SARS-CoV-2 infected versus vaccinated individuals. Regardless of ADE status or exposure type (infection or vaccination), NL63 PVs consistently showed lower neutralization activity. Overall, a clear trend of reduced neutralizing activity was observed in ADE-positive samples relative to ADE-negative ones (Figure 5).

Association of ADE with complements in SARS-CoV-2 infected samples

We used ELISA to assess the relationship between serum complement levels and ADE in samples collected during the acute phase of SARS-CoV-2 infection. Our analysis revealed significantly elevated complement levels in samples from ICU patients compared to those from severe non-ICU and mild infection cases. Despite this overall elevation, no statistically significant difference in complement levels was observed between ADE-positive and ADE-negative samples within the ICU group. However, when comparing ADE-positive ICU samples to both ADE-negative ICU samples and mild infection samples, we observed significantly higher levels of all tested complements – including C1q, C3, C3a, and C5a. The differences were highly significant, with p-values of < 0.0001, 0.0015, 0.0026, and 0.0029, respectively, when compared to ADE-negative ICU samples, and < 0.0001, <0.0001, 0.0012, and 0.0031 when compared to mild infection samples (Figure 6). Overall, the majority of ICU samples displayed elevated complement levels, irrespective of ADE activity, suggesting that severe disease may be associated with complement activation independent of ADE.

Discussion

Enhanced respiratory disease (ERD) in respiratory viral infections, a major class of ADE, is reported as a possible cause of disease severity in many respiratory illnesses, including COVID-19.[11] On the other hand, VADE is a concern with many vaccines, including respiratory viral vaccines, especially at a later stage when the serum antibody levels decrease to a point that may induce enhanced infection instead of protection.[33] Several studies reported ADE during infection FI vaccination for RSV[30] in monkeys and MERS monoclonal antibodies.[34] This study investigated ADE activity in serum samples from SARS-CoV-2 infected and/or vaccinated individuals.

Using PVs to assess antigen entry into BHK cells expressing FcgRIIa, we observed antibody-dependent enhancement (ADE) in serum samples from both SARS-CoV-2 infection and vaccination, specifically with SARS-CoV-2 PVs, but not with NL63 PVs, which utilize the ACE-2 receptor for viral entry. Notably, ADE of MERS-CoV was detected in SARS-CoV-2 infection samples, but not in vaccination samples, suggesting cross-reactivity between SARS-CoV-2 antibodies

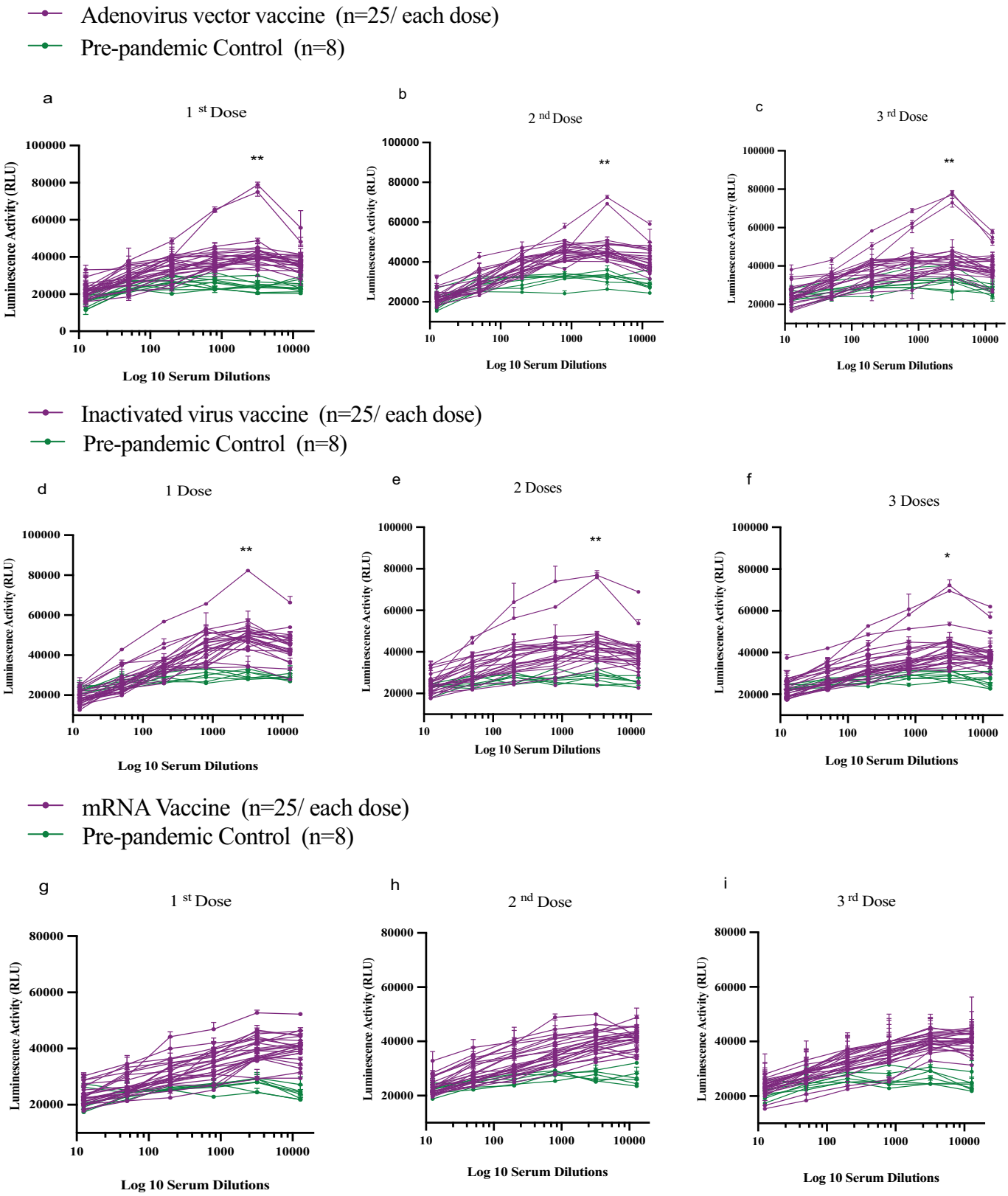

Figure 2. ADE of SARS-CoV-2 in COVID-19 vaccinated serum samples: Adenovirus vector vaccine; Dose 1(a), Dose 2 (b) and Dose 3 (c). Inactivated virus vaccine; Dose 1 (d), Dose 2 (e) and Dose 3 (f). mRNA Vaccine; Dose 1(g), Dose 2(h) and Dose 3 (i). ADE (higher luminescence) was reported as luciferase activity inside cells upon uptake of the SARS-CoV-2 PV via the Fc-RIIa receptor. Statistical analysis was performed using unpaired t test, significance is indicated by **, * and p value = 0.0294, 0.0024, 0.0321, 0.0011, 0.0053 and 0.0401.

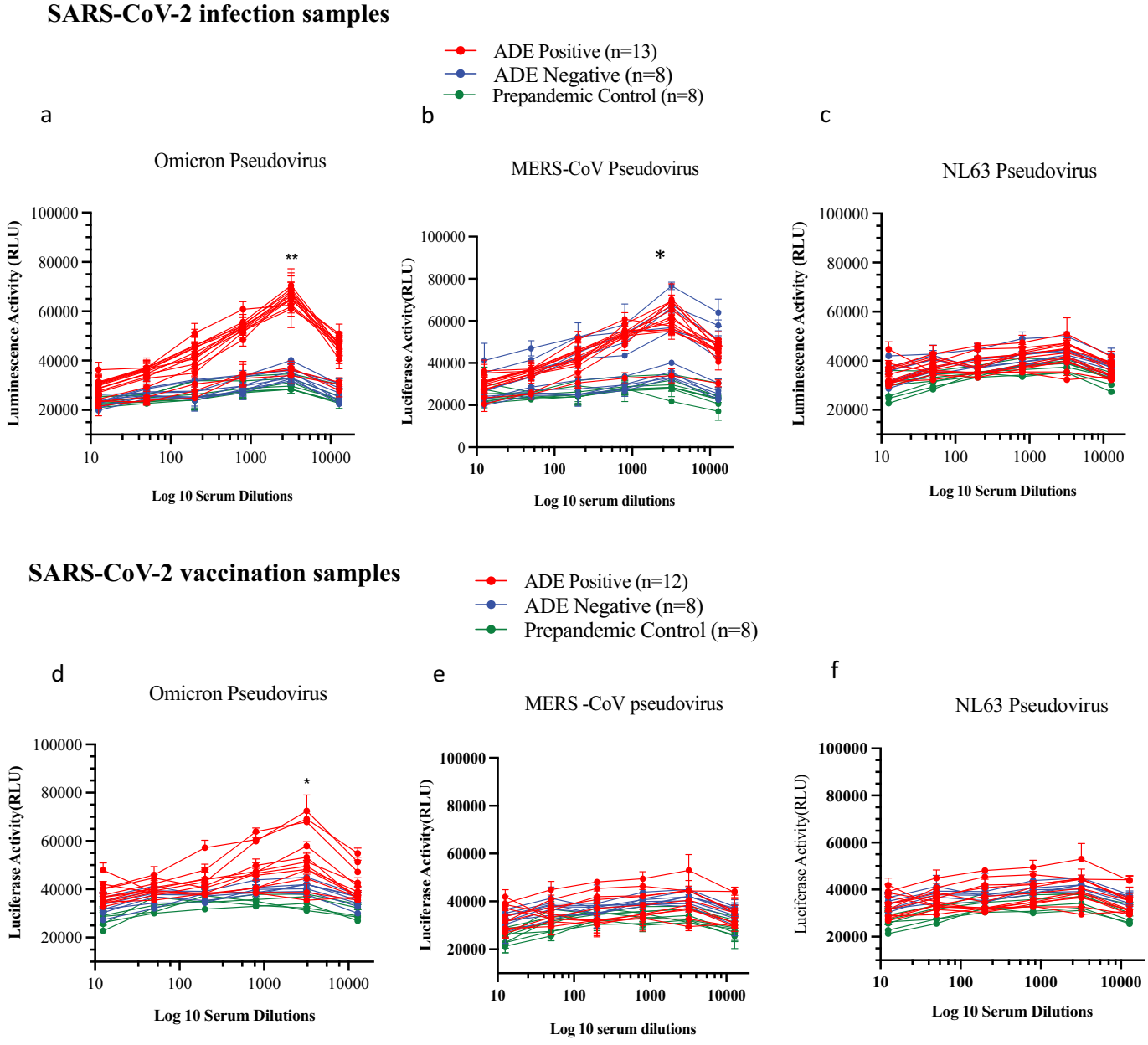

Figure 3. ADE of SARS-CoV-2 omicron, hCoV and MERS-Cov in SARS-CoV-2 infection and/or vaccination samples. ADE positive and negative samples from SARS-CoV-2 infected (all three TPs) and vaccinated (all three doses) were analyzed for ADE of SARS-CoV-2 omicron, NL63 and MERS-CoV PVs using BHK-FcgRIIa cells. ADE of SARS-CoV-2 omicron (a), NL63 (b), and MERS-CoV (c) in SARS-CoV-2 infection samples. ADE of SARS-CoV-2 omicron (d), NL63 (e), and MERS-CoV (f) in SARS-CoV-2 vaccination samples. Difference in luminescence of ADE positive and control samples were analyzed using unpaired t test, significance is indicated by **, * (p value = 0.0015 and 0.0428).

and MERS-CoV PVs. Enhanced PV entry was observed at higher serum dilutions, aligning with previous studies.[12,35] Similar findings from 2021 demonstrated cross-reactivity between camel-derived MERS-CoV antibodies and SARS-CoV-2 S trimer PVs. Although these antibodies exhibited substantial neutralization activity against SARS-CoV-2 PVs,[36] further investigations in mice, following challenge with SARS-CoV and SARS-CoV-2, concluded that cross-neutralization of live viruses may be infrequent.[37] Additionally, research indicated that the key epitopes on non-neutralizing antibodies that induce ADE are located on highly conserved spike regions,[38] with studies reporting significant similarity in these ADE-inducing epitopes between SARS-CoV and SARS-CoV-2.[39]

Our analysis revealed that antibodies mediating ADE of SARS-CoV-2 infection are more likely to be associated with disease severity. Serum samples from four patients admitted to ICU consistently demonstrated ADE of SARS-CoV-2 in samples collected at three different time points. Only one serum sample from severe patients who were not ICU-admitted showed ADE. None of the samples from mild infected patients showed ADE activity. These results support previous reports on the impact of ADE of SARS-CoV-2 on disease severity[21,40] and ADE reported in primary macrophages by SARS-CoV-2 infected serum samples.[40] Further, we characterized ADE-inducing antibodies in SARS-CoV-2 vaccination serum samples. Our results indicate that

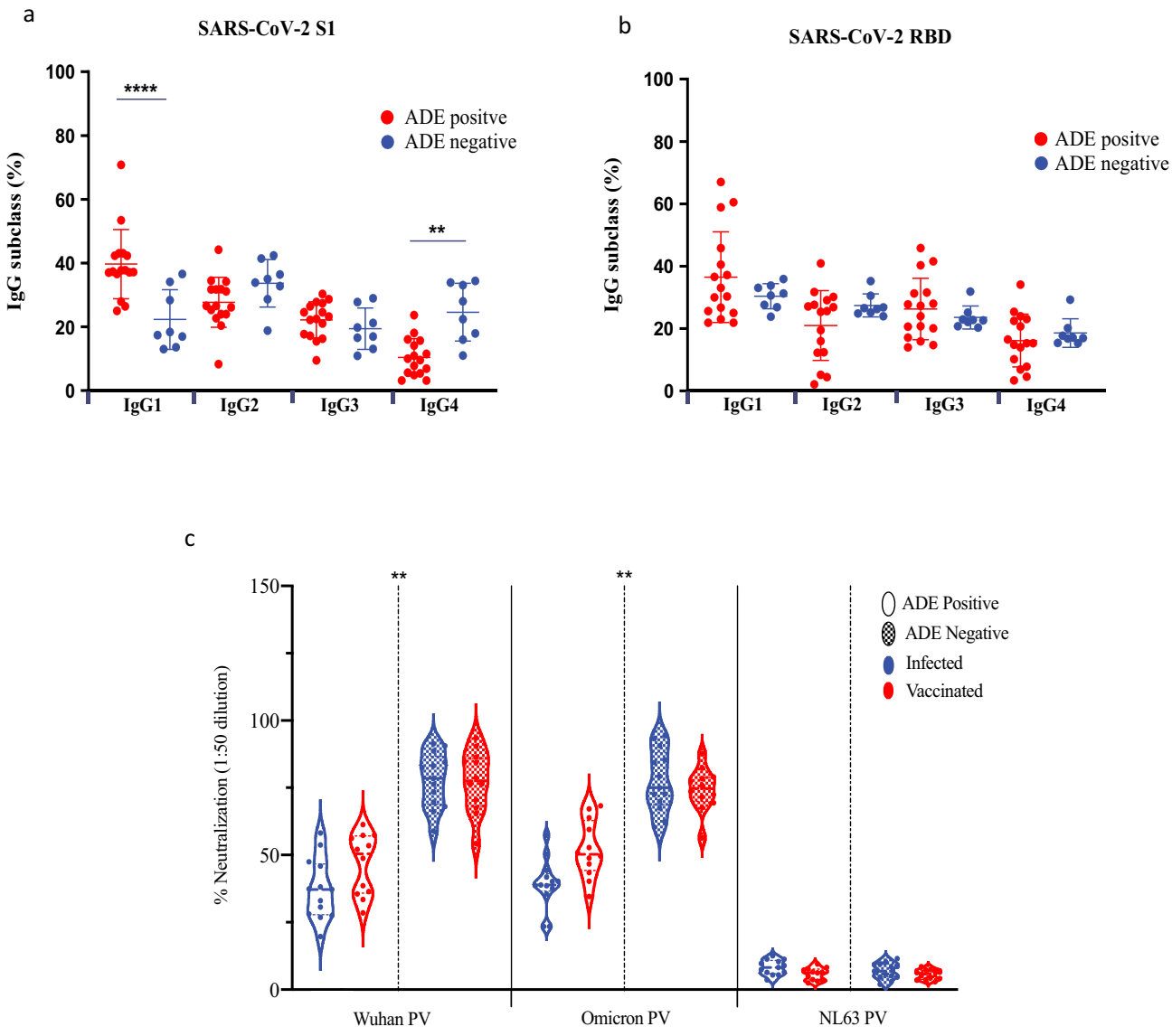

Figure 4. IgG Subtypes and neutralization in ADE positive and negative samples against different SARS-CoV-2 variants and hCoV (NL63). Levels of IgG subtypes (IgG1–4) were measured against SARS-CoV-2 RBD (a) and S1 (b) antigens. Statistical significance was determined using a one-way ANOVA. Panel (c) shows neutralization of pseudoviruses (PVs) using HEK293T cells expressing ACE2. Samples were categorized into ADE-positive and ADE-negative groups for each PV, with further classification into infected and vaccinated subgroups. The analysis included 13 ADE-positive samples from four ICU patients (collected across three timepoints), one severe non-ICU patient (one timepoint), and 12 ADE-positive samples from vaccinated individuals across three different vaccine doses. Statistical comparisons were performed using unpaired t-tests, and significance was indicated by * for p-values <0.05.

antibodies that can mediate ADE are generated in individuals vaccinated with Ad-vector and inactivated virus vaccinations; however, not after mRNA vaccination. Similar findings were reported with monoclonal antibodies against SARS-CoV-2 in Raji B and Daudi cells.[21]

Antibody subclasses and their target epitopes may define ADE activity in some patients. Though the total IgG and IgG subtypes 1 to 3 against SARS-CoV-2 S1 and RBD antigens were in a similar range (ADE-positive vs. ADE-negative samples), IgG 4 showed significantly lower titer against both proteins. The observed trend of reduced IgG2 levels in ADE-positive samples warrants further investigation in a larger cohort to confirm its significance. Previous study reports discussed association of low IgG levels in severe SARS-CoV-2 infected patients admitted to ICU.[41] Another study reported higher levels of IgG1 and IgG3 and low levels of IgG4 in SARS-CoV-2 severe infection when compared to non-severe infection.[42] Further, the neutralizing activity of serum samples against PVs was significantly lower in ADE-positive samples. These findings align with previous reports linking altered IgG profiles and reduced neutralization to severe COVID-19 outcomes. Previous *in vitro* studies using serum samples from COVID-19-infected patients reported similar findings and showed that cross-reactive but non-neutralizing antibodies can be a cause of ADE.[8,37]

Several studies reported complement activation as a distinctive feature of severe SARS-CoV-2 infection.[43,44] Our analysis to characterize the association of serum complements (C1q, C3, C3a, and C5a) to ADE showed a trend of higher complement levels in ADE-positive samples compared to ADE-negative from the ICU group; however, the

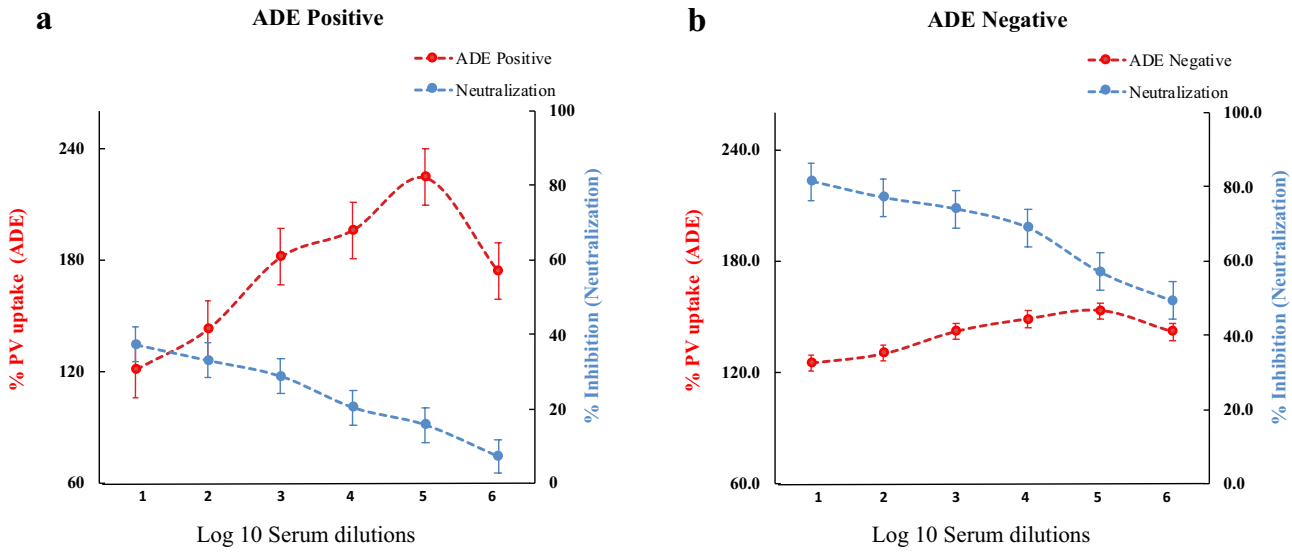

Figure 5. Association between ADE and neutralization in ADE-positive (a) ($n = 9$) and ADE-Negative (b) ($n = 11$) samples. Percentage of virus uptake (ADE) were calculated as (luminescence of serum dilutions/luminescence of pre-pandemic control) *100. Similarly, percentage neutralization was calculated as (luminescence of serum dilutions/luminescence of non-serum control) *100. Average of percent virus uptake and percent neutralization for all samples at designated dilutions were calculated and plotted accordingly.

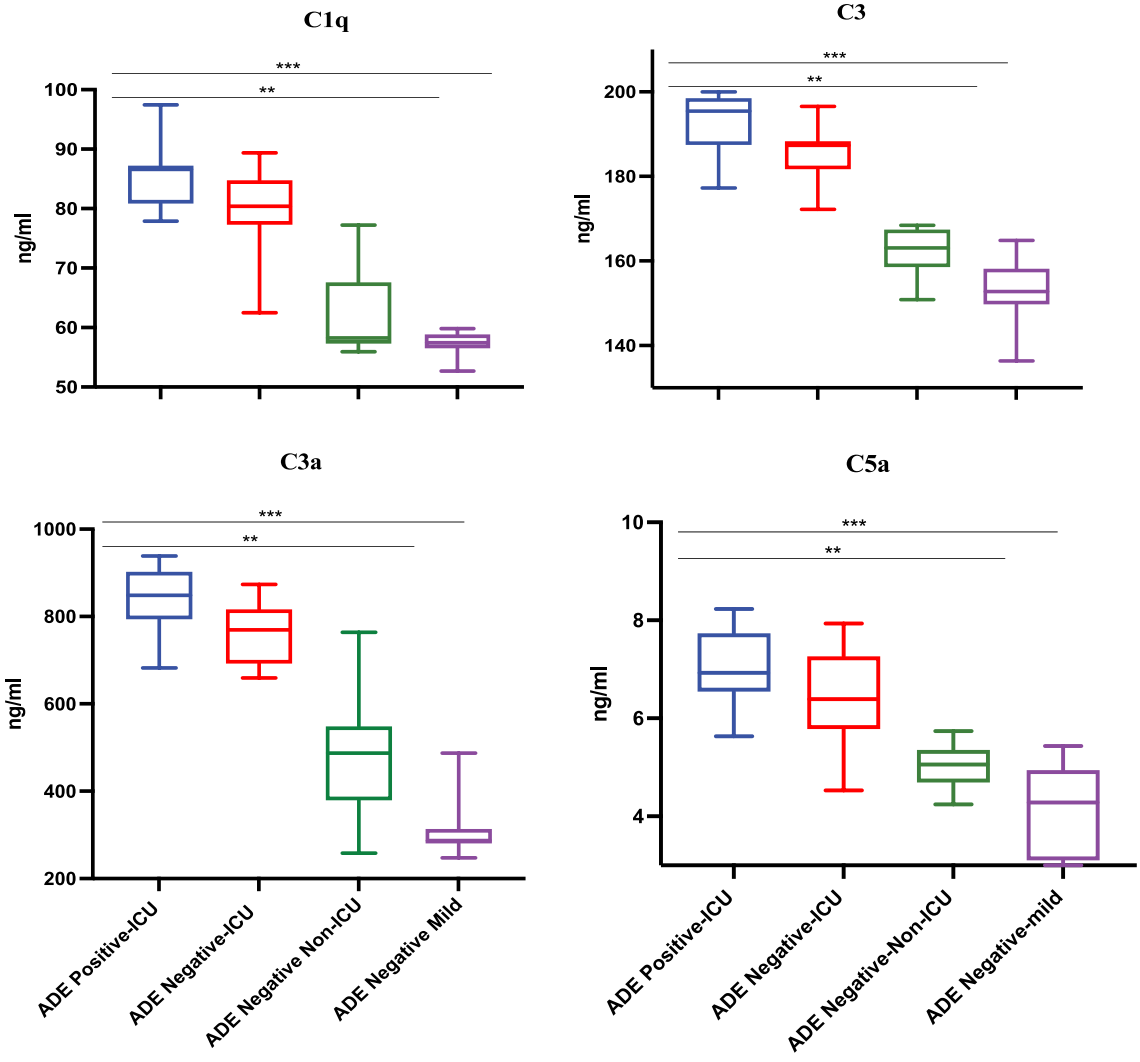

Figure 6. Association of ADE with serum complements in SARS-CoV-2 infection samples. Serum complement levels in ADE positive and negative samples from ICU, severe non-ICU and mild infection patients. Complements including C1q (a), C3 (b), C3a (c) and C5a (d) are analyzed using statistical analysis: unpaired t test and the significance is indicated by ** and ***.

difference was not statistically significant. Expectedly, we observed a significant difference in serum complement levels in ICU samples with severe non-ICU and mild infection samples. These results support previous findings reported the association of elevated complement levels with disease severity[25] However, further studies in larger cohorts may reveal the role of complements in ADE, and research to characterize the involved mechanisms may guide treatment strategies for COVID-19 patients with ERD.

Our findings suggest that ADE may become more likely later after infection recovery or vaccination, when the concentration of neutralizing antibodies generated by the primary infection has decreased to suboptimal levels. Further research into the mechanisms by which ADE-inducing antibodies contribute to severe infection could provide valuable insights into the need for ongoing vaccination against SARS-CoV-2. Additionally, the impact of preexisting immunity to other coronaviruses, including MERS-CoV and other seasonal human coronaviruses, warrants further investigation to fully understand its role in the context of SARS-CoV-2.

Conclusion

This study investigated the presence of ADE mediated by FcgRIIa in individuals exposed to SARS-CoV-2 through infection or vaccination. ADE activity was observed in serum samples from COVID-19 ICU patients and individuals vaccinated with adenovirus vector or inactivated virus vaccines, but not in those who received mRNA vaccines. Notably, ADE was also detected with MERS-CoV PVs in samples from SARS-CoV -2-infected individuals, but not in vaccinated individuals. ADE was associated with reduced neutralizing antibody activity and elevated serum complement levels. While this study characterized ADE in the context of SARS-CoV-2 and MERS-CoV, it did not assess preexisting immunity to other human coronaviruses in ADE-positive samples, particularly within the vaccinated group. Future research should aim to define the features of ADE-inducing antibodies to better understand the mechanisms underlying ADE in respiratory viral infections.

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Disclosure statement

No potential conflicts of interest are reported by the authors(s).

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Authors contributions

HMY conceptualized and designed the study. ST did the analysis. ST, MKS, HTZ, HAMA and HMY contributed to sample collection, processing, and testing. GKN, AAA, and HMY provided resources. HMY oversaw the study. AO supervised the student academically. HMY and AAJA provided funding. ST wrote the initial draft. YT and HMY reviewed and edited the manuscript. All others have contributed to data and sample gathering, and manuscript editing.

Ethical approval

Ethical approval for sample collection and processing was obtained from Qatar University (QU-IRB-1289-EA/20), the Qatar Biobank Institutional Review Board (QF-QBB-RES-ACC-0184), and Hamad Medical Corporation (HMC)(MRC-01-20-145).

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