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RESEARCH ARTICLE

Sinopharm (BBIBP-CorV) COVID-19 Vaccination in Hemodialysis Patients and Healthy Individuals: 1-year Effectiveness and Immunogenicity

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ABSTRACT

Introduction: The COVID-19 pandemic has presented significant challenges for immunocompromised populations, particularly hemodialysis patients, who are at an elevated risk for severe outcomes. Vaccination remains a critical strategy to mitigate these risks. This study evaluates the 1-year effectiveness and immunogenicity of the Sinopharm (BBIBP-CorV) COVID-19 vaccine in hemodialysis patients compared to healthy individuals, exploring correlations between dialysis parameters and vaccine-induced immunity.

Methods: This study was conducted according to the ethical principles outlined in the Declaration of Helsinki and approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences. Participants included 87 hemodialysis patients and 29 healthy controls who received two doses of the Sinopharm vaccine with a 28–30-day interval. Data were collected through in-person interviews and follow-up phone interviews at 2-, 6-, and 12-months post-vaccination. Blood samples were taken at specified intervals to measure humoral and cellular immune responses, including Anti Spike Antibody IgG, Anti receptor-binding domain(RBD) total, neutralizing antibodies, and COVID-19 interferon gamma release assay(IGRA).

Results: A total of 87 hemodialysis patients (68.97% male, mean age 53.32±15.54 years) and 29 healthy controls (27.59% male, mean age 35.72±6.19 years) were included. There was no significant difference in breakthrough infection and its severity among the groups. Breakthrough infections were observed in 5.75% of hemodialysis cases and 17.24% of healthy controls, with hemodialysis not significantly elevating the risk (P=0.08; HR: 0.34; 95% CI: 0.1, 1.16). None of the markers of immune response was associated with breakthrough infection. There was a moderate correlation between Anti-Spike and IGRA level in patients receiving the third dose.

Conclusion: The Sinopharm COVID-19 vaccine demonstrated effectiveness and induced significant immunogenicity in both hemodialysis patients and healthy individuals, with booster doses enhancing long-term immunity. This study underscores the importance of booster vaccinations in maintaining immunity, especially in immunocompromised populations.

Keywords: COVID-19, Sinopharm vaccine, hemodialysis, immunogenicity.

Introduction

The widespread administration of COVID-19 vaccines has played a vital role in mitigating the devastating health effects of the pandemic worldwide[1]. Billions of doses of COVID-19 vaccines have been administered worldwide to date, resulting in substantial reductions in COVID-19-related hospitalizations and deaths globally[2]. Multiple studies conducted in the general population have demonstrated that COVID-19 vaccines are highly effective in preventing severe illness, hospitalization, and death caused by the virus[3]. However, it remains important to continue monitoring the efficacy and safety of these vaccines in specific populations, like hemodialysis patients, that may exhibit reduced immune responses[4]. This would ensure vaccines provide robust protection across groups.

Hemodialysis patients have been shown to exhibit reduced antibody production, impaired T cell function, and altered innate immune responses compared to healthy adults[5,6]. Such immune dysfunction is associated with poorer vaccine responses, as seen with influenza and hepatitis B vaccines[7,8]. Hemodialysis patients have a higher risk of severe COVID-19 illness and death compared to the general population[9]. Early studies suggest these patients may mount a reduced antibody response to the Pfizer-BioNTech vaccine versus healthy controls[10], limited data exists regarding the efficacy of other widely administered COVID-19 vaccines, such as Sinopharm, among hemodialysis patients globally.

Evidence indicates unequal global distribution of COVID-19 vaccines, with greater coverage in high-income countries versus low- and middle-income nations[11]. mRNA vaccines from Pfizer-BioNTech and Moderna comprise the majority of doses administered in most high-income countries[10]. In contrast, inactivated vaccines, including Sinopharm, account for a substantial proportion of doses in lower-income countries, yet vaccine coverage remains below recommended levels[11,12]. This disparity is reflected in the scientific literature, with most efficacy studies focused on mRNA vaccines predominant in wealthy countries[10]. Based on our knowledge, only one study had been conducted on efficacy of Sinopharm in a systematic review of 38 studies[12]. Therefore, data on the Sinopharm vaccine and its efficacy in specific populations is limited (**Table 1**). Key high-risk populations excluded from many trials, like those on immunosuppressive therapy or with end-stage renal disease, exacerbate these evidence gaps[13]. Further research is warranted to address the lack of real-world data on globally utilized vaccines such as Sinopharm.

Table 1. Review of key studies on response of hemodialysis patients to Sinopharm COVID-19 vaccination

First Author, Year, Country	Participants	Vaccine	Investigation; Time of Sampling	Response Definition	Result
Holt et al, 2021, UAE (24)	446 HD Patients	Two doses of Sinopharm HB02 with ~21 days interval	Anti-spike antibody 21 days after D2	Anti-spike antibody >15 AU/ml	50% seroconversion in HD compared to 78% seroconversion in general population
Alirezaei et al., 2022, Iran (25)	90 HD Patients	Two doses of Sinopharm with ~4-6-week interval,	Anti-RBD IgG Before vaccination and 4-5 weeks after D2	Anti-RBD IgG ≥2.5 µg/mL	31.1% seroconversion rate in HD patients
Nafar et al., 2022, Iran (26)	100 kidney transplant patients	Two doses of Sinopharm BBIBP-CorV with ~4-week interval	Anti-spike IgG, anti-RBD IgG/IgA/IgM, and neutralizing antibodies,	Anti-spike IgG ≥8 RU/ml	58% had any positive antibody response, 46% had response in all 3 antibodies,

First Author, Year, Country	Participants	Vaccine	Investigation; Time of Sampling	Response Definition	Result
			interferon-γ release assay (IGRA), 12.3 ± 4.3 weeks after D2	Anti-RBD IgG/IgA/IgM ≥1.1 index Neutralizing antibodies ≥2.5 µg/ml interferon-γ release assay (IGRA), positive ≥200 mIU/ml	IGRA was positive in 30.7% of tested transplant recipients.
Bai et al., 2022, Pakistan (27)	50 HD patients	Two doses of Sinopharm BBIBP-CorV with ~21-day interval	Anti-S IgG, Before vaccination, 20 days after D1, 21 days after D2	Anti-S IgG ≥0.8 U/mL	72% response after D1, 94% response after D2

This prospective observational study aims to investigate the short-term immunogenicity and long-term breakthrough infections of the Sinopharm (BBIBP-CorV) vaccine in hemodialysis patients and healthy controls. Additionally, we investigated the factors associated with no response to identify patients who may require additional care after vaccination.

Material and Methods

ETHICAL CONSIDERATION

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences (IR.SBMU.UNRC.REC.1400.018). All participants provided written informed consent prior to their inclusion in the study. Participants were informed of their right to withdraw at any time without penalty or loss of benefits. Efforts were made to ensure that the study did not unfairly impact or exclude any particular community. To protect participant confidentiality, all personal data were anonymized and assigned a unique identifier code.

STUDY CONTEXT

This study was conducted in two hospitals with specialized hemodialysis units in Tehran, Iran. The hospitals are located in the northern and southern parts of Tehran, which has a population of approximately 15 million inhabitants. Center A has 20 dialysis beds, and Center B has 10. Patients were referred for maintenance hemodialysis in three shifts and used a dedicated entrance to avoid exposure to COVID-19, as both hospitals had admitted COVID-19 patients. The Sinopharm vaccine was the recommended vaccine for these patients in Iran, with other available vaccines for the general population including AstraZeneca, BarekatCov, and Sputnik.

The control group was enrolled at the Research Institute for Gastroenterology and Liver Diseases and primarily consisted of biomedical researchers with a low risk of exposure to COVID-19. A few healthcare workers were also included in the control group.

STUDY DESIGN AND RESEARCH QUESTIONS

In October 2021, patients undergoing routine hemodialysis in two hospitals were enrolled to in the study. Most of the patients had received the COVID-19 vaccine days before the start of the study, forming the HD1 cohort. A group of hemodialysis patients who had not received the COVID-19 vaccine before the start of the study was also included (HD0 cohort). The healthy cohort (C1) consisted of office personnel (N=6), biomedical

researchers (N=26), and healthcare workers (N=2). All groups, HD1, HD0, and C1, received two doses of 0.5 cc Sinopharm intramuscular vaccine with a 28-day interval between doses.

This study aims to investigate:

- Aim 1: Breakthrough infection (BTI) in HD, in comparison to healthy controls, within one year after vaccination
- Additional Investigation 1: Cox regression analysis of BTI predictors
- Aim 2: Vaccine effectiveness in provoking humoral immunogenicity in HD cases and healthy controls
- Additional Investigation 2: Correlation humoral immunogenicity with long term cellular immunity

During the study, since we faced challenges in data collection, we handled further validation analysis to see the reproducibility and validity of our result. These validation analyses include:

- Validation analysis: Congruence of humoral response at 21 days after the 2nd dose (post-D2) and 60 days post-D2
- Validation analysis: Congruence of humoral response at before vaccination and 21 days after the 1st dose (post-D1)

Inclusion criteria for HD participants were adults aged 18 years or older undergoing hemodialysis for more than 3 months. The healthy controls were adults with no chronic medical condition. Both groups included if having no contraindications to the Sinopharm vaccine, and providing informed consent. Exclusion criteria included a history of severe allergic reactions to vaccines and current acute illness at the time of enrolment, infection with COVID-19 during the immunization window (before 21 days post D2), lack of 21 days post D2 or 60 days post D2 samples, not receiving the second dose, having cancer, or deem to exit the study.

CLINICAL DATA COLLECTION

Patients were informed about the aim and design of the study, and data were collected during an in-person interview before blood sampling. The following information was gathered: demographics (age, sex, height, weight); social data (occupation, education level); clinical data on kidney disease (history of kidney transplant, ongoing immunosuppressive treatment, reason for CKD); data on hemodialysis (number of sessions per week, dialysis hours per session, years on hemodialysis); previous COVID-19 history (infection history, diagnosis method, date of infection, management setting, COVID-19 history in housemates); response to other vaccinations (co-vaccination, prior vaccination response, Hepatitis B vaccination); drug history (corticosteroids, MMF/MPA, mTOR-inhibitor); past medical history (diabetes, hypertension, ischemic heart disease, COPD, asthma, allergies, cerebrovascular accident, cancer, physical disability, polycystic kidney disease, glomerulonephritis, vasculitis, liver cirrhosis); habitual history (smoking, pack-year, alcohol, opium); and available laboratory data. Data collection was performed using pre-defined form and during phone interview.

FOLLOW-UP

Phone interviews were conducted at 2 months, 6 months, and 12 months after the first vaccination. The following data were collected during the phone interviews: vaccine adverse events (injection site, systemic reactions, anaphylaxis, treatment received for adverse events), COVID-19 infection between the first dose and 21 days post-second dose, and breakthrough infections (diagnosis method, date, and management setting). Data on adverse events and breakthrough infections were verified through review of medical records when available.

BLOOD SAMPLING TIMELINE

Blood samples were collected from the HD0 cohort before vaccination and on days 1-2 and 20-22 of each vaccination. For the HD1 and C1 cohorts, samples were collected on days 20-22 after each vaccination. Both HD0 and HD1 cohorts were sampled 60-65 days after the second dose. Blood samples were collected at the earliest possible time, before dialysis, from the HD1 and HD0 cohorts. The blood sampling and interview timeline for each cohort is illustrated in **Figure 1**.

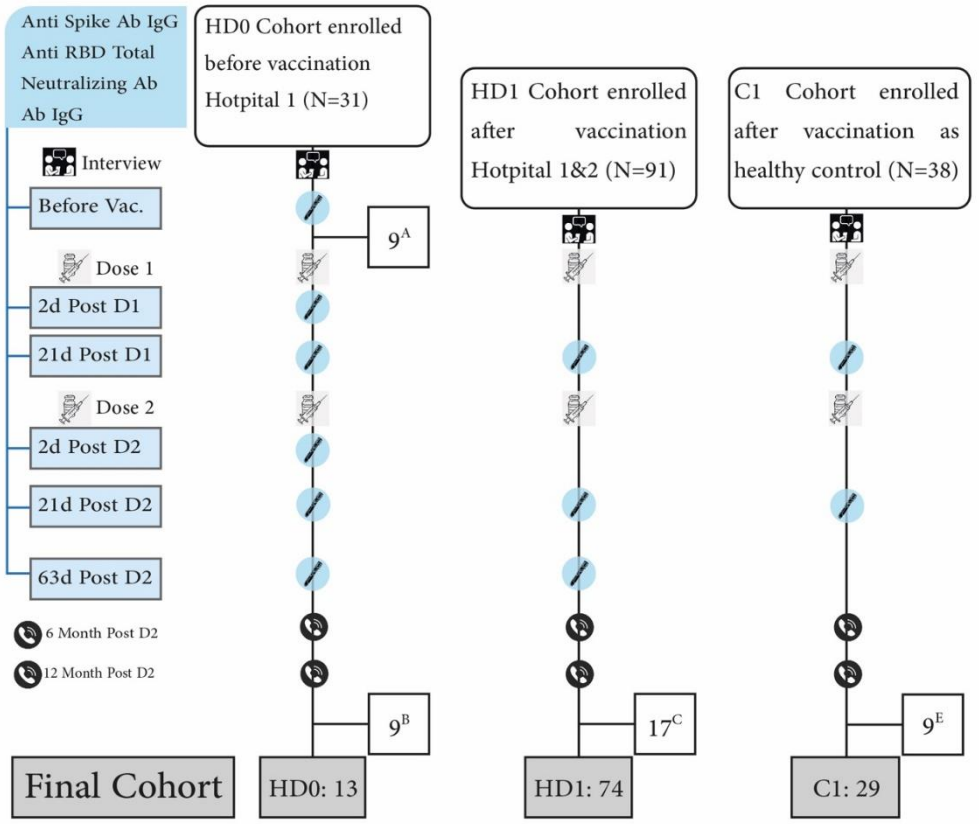

Figure 1. Study timeline regarding blood sampling, data collection, and interview. Figure caption. HD0: hemodyalsis patients included in the study before injection of first vaccine,. HD1 :hemodyalsis patients who already recived first dose of vaccination at the time of inclusion. C1: The control group included healthy indivisuals. Numbers in side boxes are participients excluded during study due to different reasons.

In our study, we evaluated the humoral response to SARS-CoV-2 vaccination at three time points for all HD cohort: 21 days post first dose (D1), 21 days post second dose (D2), and 60 days post second dose (D2), as well as before vaccination (D0), and 1-2 day before D1, 1-2 day before D2, for HD cases who hasn't been vaccinate at the time of enrolment. This timeline was chosen to capture the dynamics of the antibody response immediately following initial immunization and subsequent booster administration to understand kinetics of humoral response. Healthy individuals were sampled at 21 days post D1 and 21 days post D2 for comparison.

Additionally, we investigated T-cell responses 365 days post second dose (D2) using the Interferon Gamma Release Assay (IGRA). Research has shown that memory T-cells can persist for extended periods, with studies demonstrating the presence of memory T-cells specific to other coronaviruses years after infection. Emerging evidence suggests that a significant proportion of patients who do not mount an antibody response to SARS-CoV-2 vaccines. The IGRA assay, which measures plasma Interferon Gamma (IFN-γ) production, has shown strong correlation with the percent of IFN-γ-producing activation-induced marker (AIM) positive T cells identified by flow cytometry. This supports IGRA as a robust, clinically feasible alternative for assessing T-cell responses in B-cell depleted patients.

HUMORAL IMMUNITY

Fresh blood samples were collected in two 6 mL heparinized EDTA tubes. Blood collection was performed before the start of dialysis in most cases, or within the first hour of dialysis. Samples were stored at 2-8°C in a refrigerator if there was a delay in processing, ensuring processing occurred within 2-8 hours. Samples were transported to the laboratory maintaining the 2-8°C temperature using a cooling box. Blood in heparinized tubes was gently mixed to prevent clotting. Samples were centrifuged, and plasma was aliquoted into cryovials (500 µL per vial). Plasma samples were

stored at -80°C until further analysis. Each cryovial was labelled with a unique participant identifier, the date of collection, and sampling interval (D0, 2-D1, 21-D1, 2-D2, 21-D2, 60-D2).

Plasma samples stored at -80°C were carefully defrosted by placing the cryovials on ice and allowing them to thaw gradually for 1-2 hours. Once fully thawed, the samples were gently mixed by inverting the tubes several times. Following this, the ELISA kit procedures were initiated according to the manufacturer's instructions.

The Elecsys® Anti-SARS-CoV-2, Quanti SARS-CoV-2 Anti-Spike IgG ELISA Kit, Quanti SARS-CoV-2 Anti-RBD IgG ELISA Kit, and SARS-CoV-2 Neutralizing Antibody ELISA Kit were used to investigate COVID-19 IgG, anti-spike IgG, anti-RBD IgG, and neutralizing antibodies, respectively. Detailed information on the ELISA kits is presented in Supplementary Table S1.

The responder group was defined as having positive Anti-Spike IgG 21 days post-second dose (D2). The cut-off value was set at 8 RU/mL as per the diagnostic kit instructions. Previously provoked immunity (before vaccination) was defined as having positive Anti-Spike IgG before vaccination or 21 days post-first dose (D1).

CELLULAR IMMUNITY

The whole blood sample were collected and transferred in a cold chain (2-8 degree) in two EDTA tubes. The test took places at the same day of sampling within 2-8 hours of blood sampling. EUROIMMUN SARS-CoV-2 Quan-T-Cell IGRA used (**Supplemantary Table S1**). According to the manufacturer's instructions (SARS-CoV-2 IGRA stimulation tube set, Euroimmun, Lübeck, Germany), lithium heparinized blood from each patient was incubated for 21 hours at 37°C in the three supplied tubes. Subsequently, the samples were centrifuged at 1300× g for 10 minutes, and the plasma was then frozen. In the testing procedure, T-cells in the patient samples are stimulated using spike protein-based antigens provided in the tubes, and the released IFN-γ is measured using a fully automated quantitative ELISA, following the manufacturer's protocol.

STATISTICAL ANALYSIS

Numerical data were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Categorical data were presented as frequencies and percentages. Paired sample t-tests were used when normality test was satisfied, and non-parametric test of Wilcoxon signed ranked test was used when the data is not normality distributed among repeated measures. In the same manner, independent t-test and Mann Whitney test was used to compare categorical variables between two independent samples. 95CI was calculated using the critical value of the t-distribution for a 95% confidence interval, corresponding to the 97.5th percentile for independent and paired t-test, as well as Wilcoxon, while for Mann Whitney test the bootstrapping method was used to calculate 95%CI (bootstrap =1000, alpha=0.05). Chi-square was used to compare categorical data in two time-points or between two samples. A Cox proportional hazards model was employed to investigate the association between various covariates and the risk of BTIs in the study population. The analysis was performed using the lifelines library in Python. The proportional hazards assumption was assessed through visual inspection of Schoenfeld residuals and the scaled Schoenfeld residual test. Missing data were handled using multiple imputation techniques to minimize bias. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant. Statistical analyses and visualizations were conducted using Python (version 3.8) libraires of seaborn, matplotlib, SciPy, pandas, and lifelines. No imputation or normalization was use during analysis of the immunogenicity and HR.

Results:

BASIC CHARACTERISTICS AND ADVERSE REACTIONS

A total of 87 HD patients (68.97% male) with mean age of 53.32±15.54 years and 29 (27.59% male)

healthy controls with mean age of 35.72±6.19 years were included in the final analysis, receiving first dose (D1) and second dose (D2) of Sinopharm vaccine with 28-30 days interval. **Table 2** shows the participants' basic characteristics and medical history. The education level of controls was higher than that of HD cases (P<0.001).

Table 2. Basic characteristics, clinical history, COVID-19 infection before vaccination, and dialysis protocol for hemodialysis (HD) cases and healthy controls.

	Total	HD case	Healthy control	P value
Male Gender	58.62% (68 / 116)	68.97% (N= 60 / 87)	27.59% (N= 8 / 29)	0.001
Age (Year)	48.92±15.76 (N= 116)	53.32±15.54 (N= 87)	35.72±6.19 (N= 29)	0.001
BMI (kg/m2)	24.61±5.09 (N= 109)	24.88±5.5 (N= 85)	23.66±3.15 (N= 24)	
Past Medical History				
Prednisolone Use	3.45% (4 / 116)	4.6% (N= 4 / 87)		
DM	29.31% (34 / 116)	39.08% (N= 34 / 87)		
HTN	56.03% (65 / 116)	74.71% (N= 65 / 87)		
IHD	31.03% (36 / 116)	41.38% (N= 36 / 87)		
COPD	1.72% (2 / 116)	2.3% (N= 2 / 87)		
Asthma	1.72% (2 / 116)	2.3% (N= 2 / 87)		
Allergy	9.48% (11 / 116)	8.05% (N= 7 / 87)	13.79% (N= 4 / 29)	0.583
CVA	5.17% (6 / 116)	6.9% (N= 6 / 87)		
Physical disability	4.31% (5 / 116)	5.75% (N= 5 / 87)		
History of Kidney Transplant	16.09% (14 / 87)	16.09% (N= 14 / 87)		
Years on Kidney Transplant	9.47±9.29 (N= 17)	9.47±9.29 (N= 17)		
Immunosuppressive treatment	4.6% (4 / 87)	4.6% (N= 4 / 87)		
ESRD Etiology				
DM	33.33% (29 / 87)	33.33% (N= 29 / 87)		
Unknown	18.39% (16 / 87)	18.39% (N= 16 / 87)		
HTN	18.39% (16 / 87)	18.39% (N= 16 / 87)		
GN	12.6% (11 / 87)	12.6% (N= 11 / 87)		
ADPKD	5.75% (5 / 87)	5.75% (N= 5 / 87)		
Other	11.54% (10/87)	11.54% (10/87)		
Dialysis Plan				
Dialysis hour/week	11.09±2.15 (N= 87)	11.09±2.15 (N= 87)		
Years on dialysis	7.39±11.18 (N= 86)	7.39±11.18 (N= 86)		
COVID-19 History				
COVID-19 infection	30.17% (35 / 116)	32.18% (N= 28 / 87)	24.14% (N= 7 / 29)	1
Number of COVID-19 infection	1.17±0.45 (N= 35)	1.21±0.5 (N= 28)	1.0±0.0 (N= 7)	
Diagnosis Method				0.642
PCR	68.57% (24 / 35)	67.86% (N= 19 / 28)	71.43% (N= 5 / 7)	
Clinical	22.86% (8 / 35)	21.43% (N= 6 / 28)	28.57% (N= 2 / 7)	
CT	8.57% (3 / 35)	10.71% (N= 3 / 28)		
Management				0.017
Home	47.06% (16 / 34)	35.71% (N= 10 / 28)	100.0% (N= 6 / 6)	
Ward	41.18% (14 / 34)	50.0% (N= 14 / 28)		
ICU	11.76% (4 / 34)	14.29% (N= 4 / 28)		
History of COVID-19 in roommate	19.83% (23 / 116)	22.99% (N= 20 / 87)	10.34% (N= 3 / 29)	0.226

There was no significant difference in previous COVID-19 infection, with 32.18% of HD cases and 24.14% of healthy controls having been infected with COVID-19 at least once. However, 21.43% and 28.57% of these infections were not confirmed by further tests in HD cases and healthy controls, respectively. The severity of previous infection was higher in HD cases, with 14.29% requiring ICU admission and 50.0% requiring ward admission, whereas all controls were managed at home.

Supplementary Table S2 displays adverse reactions to D1 and D2 vaccination. No severe adverse reactions occurred. Injection site pain was the most common adverse event in D1 (11.21%) and D2 (7.76%), and there were no reports of anaphylaxis reactions, hospitalization due to vaccination, or adverse events compromising individuals' daily activities.

COVID-19 BREAKTHROUGH INFECTION

During the immunization window, which is defined as the interval between D1 administration and 21 days post D2, a total of 6 individuals were infected with COVID-19. All cases were confirmed through additional CT or PCR testing. Among them, two patients were admitted, and were subsequently discharged. These 6 patients, all belonging to the HD case group, were excluded from the immunogenicity analysis. **Supplementary Table S3** provides an overview of COVID-19 infections occurring during the immunization window or within 21 days after D2, i.e., breakthrough infections.

Breakthrough infections was observed in 5.75% (5/87) of HD cases and 17.24% (5/29) of healthy controls. As depicted in **Figure 2**, the data suggest that HD does not significantly elevate the risk of breakthrough infections; however, there is a trend towards a decrease in risk that is not statistically significant (P=0.08; HR: 0.34; 95% CI: 0.1, 1.16). Notably, two HD patients declined further confirmatory PCR tests; however, due to their strong alignment with COVID-19 infection symptoms and the absence of alternative explanations, they were not excluded from the analysis (see Figure S1 for result considering test-validated COVID-19 BTI). Furthermore, all cases of breakthrough infection ultimately resolved, with one HD patient and one healthy control requiring admission. Importantly, no instances of COVID-19-related deaths, intubations, or ICU admissions occurred.

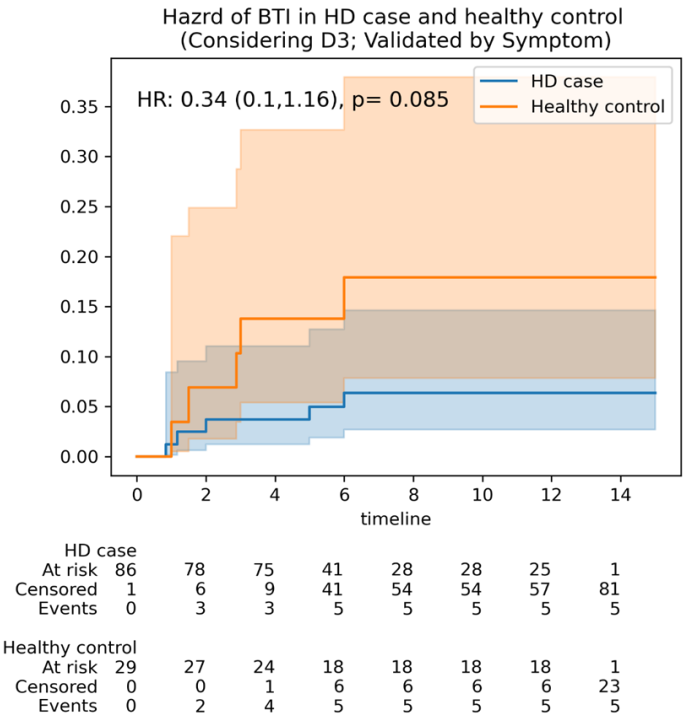

Figure 2. Cumulative density plot illustrating the chance of breakthrough infection (validated by clinician confirmed diagnosis) in HD cases and healthy controls, along with its hazard ratio (HR) considering HD cases as the reference.(The administration of the third dose and the last follow-up were treated as censoring events, while breakthrough infections were considered as events.)

PREDICTORS OF BREAKTHROUGH INFECTION

Univariate Cox regression demonstrates no significant association between antibody seroconversion (including Anti-Spike, neutralizing and anti-RBD antibodies) and breakthrough infection. As **Table 3** shows, the only statistically significant associations with breakthrough infections were related to injection site and systemic adverse events of vaccination. Headache after the first dose (D1) was strongly associated with increased immunogenicity (HR = 14.94, 95% CI: 3.11-71.79, p = 0.001), while malaise after D1 was associated with decreased immunogenicity (HR = 0.14, 95% CI: 0.03-0.65, p = 0.012). Injection site pain/swelling after the second dose (D2) was also associated with decreased immunogenicity (HR = 0.13, 95% CI: 0.02-0.77, p = 0.025). Other variables, including demographic factors, medical history, and history of previous infection, did not show statistically significant associations with immunogenicity outcomes. These findings suggest that certain post-vaccination symptoms may be indicative of the immune response strength in this population.

Table 3. Univariate Cox regression of breakthrough infection

	P-value	HR (95CI)
Age (years)	0.812	0.99 (0.94, 1.05)
Gender (female; ref: male)	0.175	3.45 (0.58, 20.62)
BMI (kg/m2)	0.243	1.1 (0.94, 1.28)
History of Kidney Transplant (No; ref: Yes)	0.546	25.95 (0, +100)
History of COVID-19 infection (No; ref: Yes)	0.206	0.32 (0.05, 1.89)
Number of COVID-19 infection (N)	0.07	5.27 (0.87, 31.75)
History of COVID-19 in household (No; ref: Yes)	0.343	0.42 (0.07, 2.52)
History of DM (No; ref: Yes)	0.369	2.73 (0.31, 24.45)
History of HTN (No; ref: Yes)	0.096	4.57 (0.76, 27.37)
History of IHD (No; ref: Yes)	0.844	1.2 (0.2, 7.16)
History of Allergies (No; ref: Yes)	0.338	0.34 (0.04, 3.07)
History of CVA (No; ref: Yes)	0.674	0.04 (0, +100)
Smoking (non-smoker; ref: smoker)	0.54	0.03 (0, +100)
Adverse event after D1 (No; ref: Yes)	0.662	0.71 (0.15, 3.33)
Injection site pain/swelling D1 (No; ref: Yes)	0.084	3.29 (0.85, 12.73)
Malaise D1 (No; ref: Yes)	0.012	0.14 (0.03, 0.65)
Headache D1 (No; ref: Yes)	0.001	14.94 (3.11, 71.79)
Fever D1 (No; ref: Yes)	0.561	22.55 (0, +100)
Adverse event after D2 (No; ref: Yes)	0.558	0.52 (0.06, 4.65)
Injection site pain/swelling D2 (No; ref: Yes)	0.025	0.13 (0.02, 0.77)
Malaise D2 (No; ref: Yes)	0.81	20.89 (0, +100)
Headache D2 (No; ref: Yes)	0.865	20.48 (0, +100)
Fever D2 (No; ref: Yes)	0.768	21.31 (0, +100)
Anti-RBD 21-D1 (index)	0.39	0.03 (0, 95.11)
Anti-RBD 21-D2 (index)	0.481	0.04 (0, +100)
Anti-Spike 21-D1 (RU/ml)	0.358	0.03 (0, 62.34)
Anti-Spike 21-D2(RU/ml)	0.423	0.03 (0, +100)
Neut-Ab 21-D1 (micg/ml)	0.374	0.37 (0.04, 3.31)
Neut-Ab 21-D2 (micg/ml)	0.419	0.41 (0.05, 3.63)
IgG 21-D1 (index)	0.768	0.96 (0.72, 1.27)
IgG 21-D2 (index)	0.653	1.06 (0.83, 1.34)

IMMUNOGENICITY IN HEMODIALYSIS

Figure 3 illustrates the immunogenicity of the Sinopharm COVID-19 vaccine in two HD patient cohorts (HD0 and HD1), excluding 35 patients with prior COVID-19 exposure. Both cohorts exhibited a modest increase in antibody levels after the first dose, with a more pronounced response following the second dose. The HD0 cohort demonstrated a particularly marked enhancement, potentially due to their naïve immune status. While both groups had antibody levels above baseline throughout the study period, a gradual decline was observed over time. **Supplementary Figure S2** reveals that the HD1 cohort experienced a more rapid decrease in antibody levels, possibly attributable to immune exhaustion or compromised long-term immune response capabilities in HD patients. These findings underscore the vaccine's ability to elicit an immune response in immunocompromised individuals, while highlighting the potential need for booster doses or doubling the dose to maintain protection in this population.

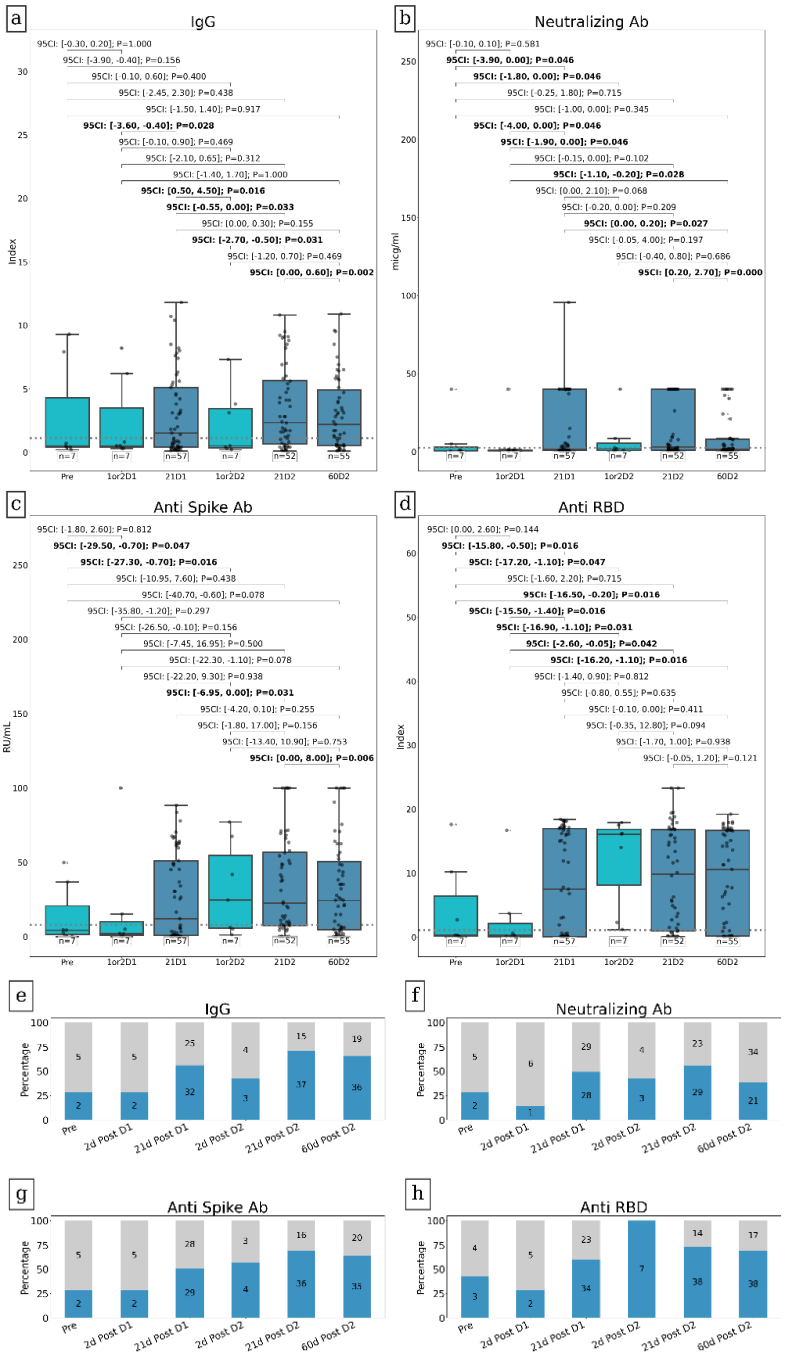

Figure 3. The quantitate results of immunogenicity in six-time points in the haemodialysis patients (Wilcoxon test)

IMMUNOGENICITY IN HEMODIALYSIS: PREVIOUS COVID-19 VERSUS NO EXPOSURE

Figure 4 compares immunogenicity between HD patients with and without prior COVID-19 infections following Sinopharm (BBIBP-CorV) vaccination. Patients with previous infections exhibited significantly higher post-vaccination antibody levels, including IgG, anti-spike, and neutralizing antibodies, compared to COVID-19 naïve patients. The disparity in antibody levels was most pronounced at early post-vaccination time points, suggesting pre-existing immune memory facilitates a more rapid and robust response. Over time, antibody levels in both groups converged, with previously infected individuals maintaining slightly higher levels. The vaccine effectively boosted immunity in previously infected patients while also providing substantial protection to naïve individuals, albeit at a slower rate. These results highlight the importance of vaccination regardless of prior infection status and suggest the need for tailored vaccination strategies, potentially including booster or higher doses, especially for COVID-19 naïve HD patients.

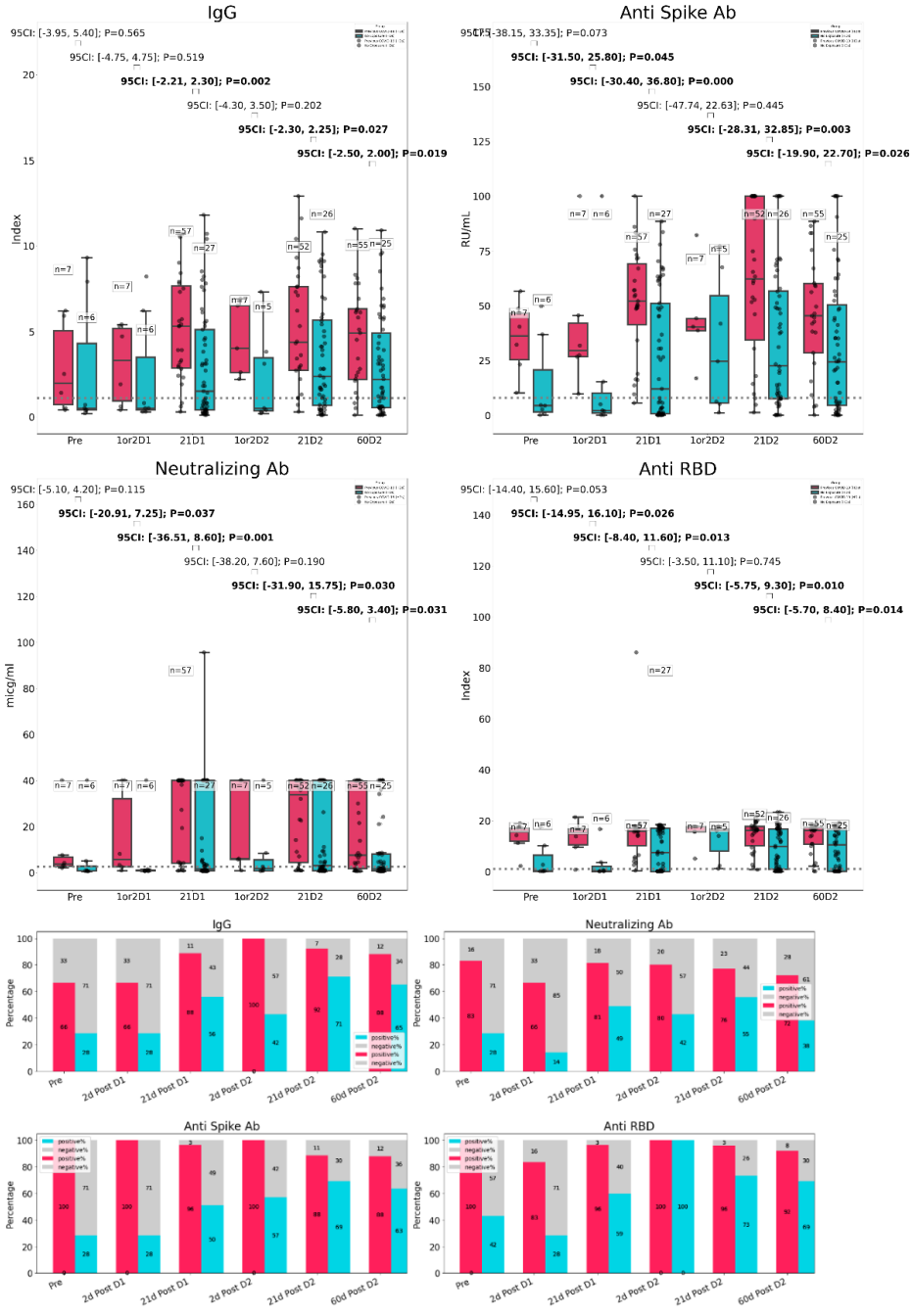

Figure 4. Comparison of immunogenicity between HD cases with and without prior COVID-19 infection

COMPARISON OF IMMUNOGENICITY BETWEEN HEMODIALYSIS PATIENTS AND HEALTHY COHORTS

Figure 5 illustrates the comparative immunogenicity of the Sinopharm COVID-19 vaccine in HD patients and healthy controls. Both groups exhibited significant immune responses post-vaccination, with healthy individuals showing stronger and more rapid antibody production. Neutralizing antibody levels were notably lower in HD patients, with a more rapid decline over time. At 21 days post-second dose (D2), healthy controls demonstrated significantly higher antibody titres across all parameters, with anti-spike antibody levels nearly doubling those in HD patients. Over the subsequent 60 days, HD patients experienced a steeper decline in antibody levels. These findings suggest a potentially compromised vaccine efficacy in HD patients, likely due to their underlying health conditions and ongoing treatments. The results underscore the need for tailored vaccination strategies, including earlier, more frequent or higher booster doses, for HD patients to ensure adequate protection against COVID-19.

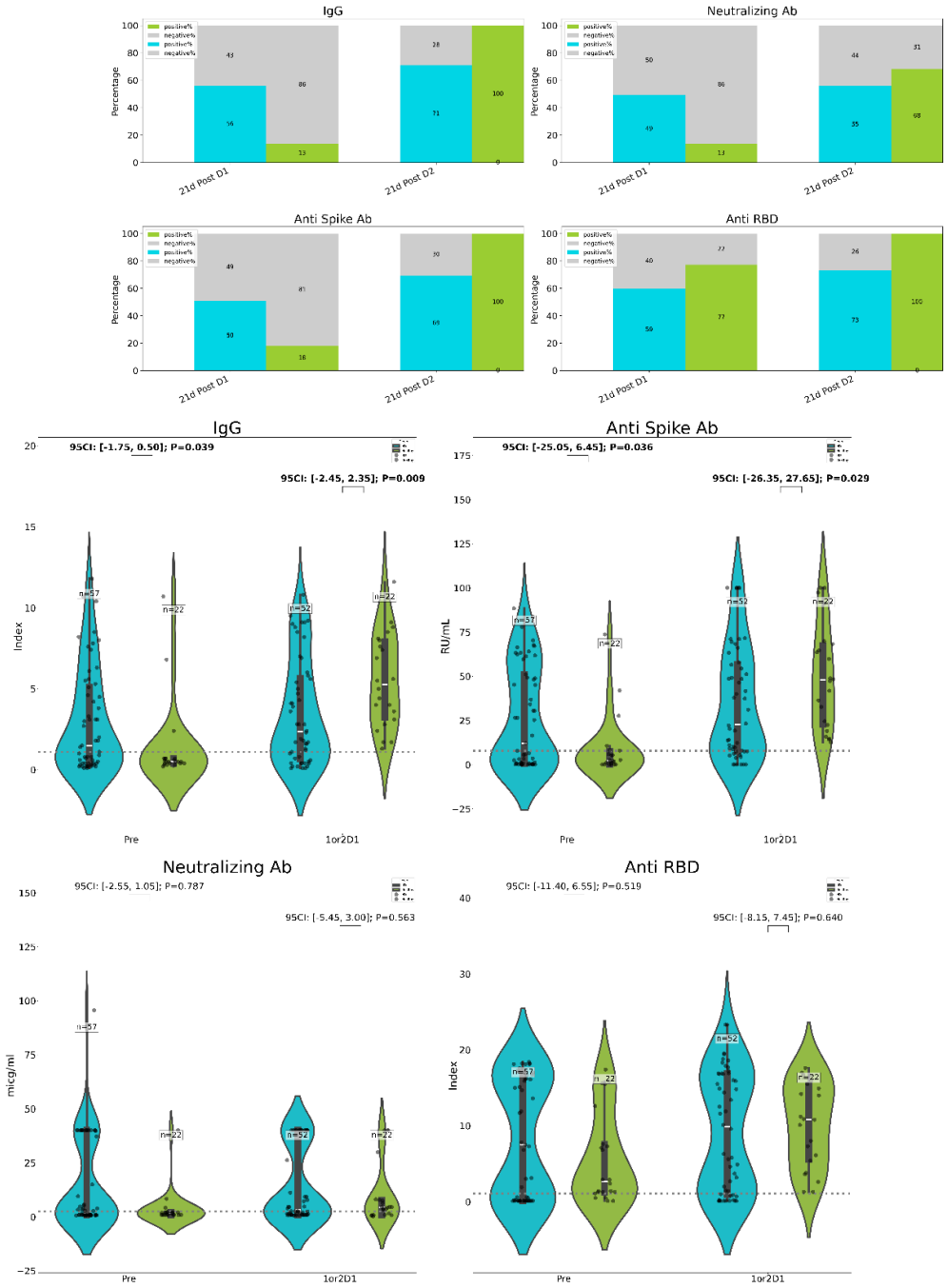

Figure 5. Comparison of immunogenicity responses between hemodialysis patients and healthy individuals after COVID-19 vaccination

COMPARISON OF MID-TERM HUMORAL IMMUNOGENICITY AND LONG-TERM CELLULAR IMMUNITY

Figure 6 depicts the correlation of long-term cellular immunity, 1-year post D2 IGRA, and mid-term humoral immunity, 1-month post D2 profile, excluding patient with COVID-19 infection before vaccination. The correlation is moderate for anti-spike in patients with D3 vaccination. However, IgG showed correlation with IGRA in patients without D3 vaccination.

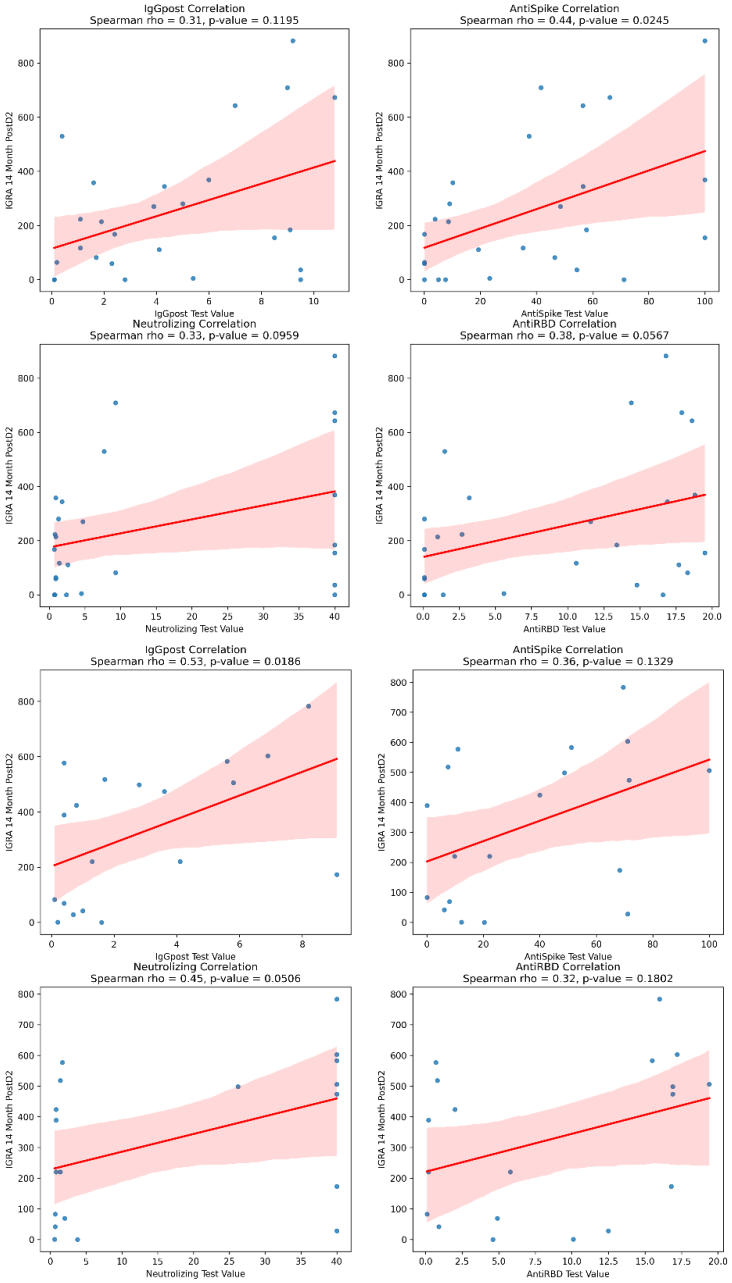

Figure 6. Correlation of 1-year IGRA with 1-month hemural immunity post D2 in patients who did (upper pannel) and did not (lower pannel) recived third dose

Discussion

The COVID-19 pandemic has had a profound impact on global health, with vulnerable populations such as patients with chronic kidney disease and those undergoing hemodialysis (HD) being particularly at risk[14,15]. The development and deployment of effective vaccines against SARS-CoV-2 have been crucial in mitigating the impact of the pandemic; however, the effectiveness and immunogenicity of COVID-19 vaccines in HD patients remain unclear. This study aimed to address this knowledge gap by investigating the effectiveness, immunogenicity, and long-term outcomes of the Sinopharm (BBIBP-CorV) COVID-19 vaccine in HD patients compared to healthy individuals over a one-year period.

One of the key findings of our study was that HD patients did not have a significantly elevated risk of breakthrough infections (BTIs) compared to healthy controls, even a trend towards a decreased risk was observed. The incidence of BTIs was 5.75% in HD patients and 17.24% in healthy controls, with no statistically significant difference between the two groups (P=0.08; HR: 0.34; 95% CI: 0.1, 1.16). These results are in line with previous studies that have reported similar BTI rates in HD patients and the general population[16,17]. The trend towards a lower risk of BTIs in HD patients, while not reaching statistical significance, may be attributed to several factors. HD patients are often under close medical supervision and may adhere more strictly to preventive measures such as mask-wearing and social distancing. Additionally, the immunocompromised state of HD patients[18], may lead to a lower viral load and reduced transmission risk.

One of the key findings of our study was the significant differences in the humoral immune response at various time points after vaccination in HD patients. We observed significant increases in IgG levels from pre-vaccination to 21 days post-first dose (D1), as well as between 2 days post-D1 and 21 days post-D1. Furthermore, significant differences were found between 21 days post-D1 and 2 days post-second dose (D2), 2 days post-D2 and 21 days post-D2, and 21 days post-D2 and 60 days post-D2. These findings suggest that the Sinopharm vaccine elicits a robust IgG response in HD patients, which continues to increase over time and is maintained for at least 60 days after the second dose.

Similarly, Anti-Spike antibody levels showed significant increases from pre-vaccination to 21 days post-D1, 2 days post-D2, and 60 days post-D2. Significant differences were also observed between 21 days post-D1 and 21 days post-D2, as well as between 21 days post-D2 and 60 days post-D2. These results indicate that the Sinopharm vaccine induces a strong Anti-Spike antibody response in HD patients, which is maintained and even increases over time.

Neutralizing antibodies, which play a crucial role in preventing viral entry and infection[19], also showed significant differences between 21 days post-D1 and 60 days post-D2, as well as between 21 days post-D2 and 60 days post-D2. These findings suggest that the Sinopharm vaccine induces a potent neutralizing antibody response in HD patients, which continues to increase over time and may provide long-lasting protection against SARS-CoV-2 infection.

Finally, Anti-RBD antibodies, which target the receptor-binding domain of the SARS-CoV-2 spike protein and are associated with neutralizing activity[20], showed significant increases from pre-vaccination to 2 days post-D2 and 60 days post-D2. Significant differences were also found between 2 days post-D1 and 2 days post-D2, 21 days post-D2, and 60 days post-D2. These results indicate that the Sinopharm vaccine elicits a robust Anti-RBD antibody response in HD patients, which increases over time and may contribute to the overall protective effect of the vaccine.

In addition to the humoral immune response, our study also investigated the cellular immune response and its relationship with humoral immunity, stratified by the receipt of a third vaccine dose. We found that there was no significant difference in the interferon-gamma release assay (IGRA) response at 14 months post-D2 between patients who received a third dose and those who did not. However, when analysing the correlation between humoral and cellular immune responses in patients who received a third dose, we found significant positive correlations between IgG, Anti-Spike antibody, neutralizing antibody, and Anti-RBD levels with IGRA at 14 months post-D2. These correlations suggest that the third vaccine dose may enhance the coordination between humoral and cellular immune responses, potentially providing more comprehensive and long-lasting protection against SARS-CoV-2 infection.

In contrast, patients who did not receive a third vaccine dose showed no significant correlations between IgG, Anti-Spike antibody, neutralizing

antibody, or Anti-RBD levels with IGRA at 14 months post-D2. This finding highlights the potential benefit of administering a third vaccine dose to HD patients to maintain and strengthen the relationship between humoral and cellular immunity over time.

The results of our study have important implications for the management of COVID-19 vaccination in HD patients. The robust humoral immune response elicited by the Sinopharm vaccine, as evidenced by significant increases in IgG, Anti-Spike antibody, neutralizing antibody, and Anti-RBD levels, suggests that this vaccine is effective in inducing a protective immune response in HD patients. Moreover, the significant differences observed between various time points post-vaccination indicate that the immune response continues to evolve and strengthen over time, potentially providing long-lasting protection against SARS-CoV-2 infection.

The finding that a third vaccine dose may enhance the coordination between humoral and cellular immune responses in HD patients is particularly relevant, as it suggests that additional doses may be necessary to maintain optimal protection in this vulnerable population. Recent studies emphasize the crucial role of a third vaccine dose in enhancing both humoral and cellular immune responses in hemodialysis (HD) patients. This additional dose significantly boosts the production of neutralizing antibodies, which are essential for protecting against SARS-CoV-2 and its variants[21,22]. The third dose also markedly improves T-cell responses, particularly the activity of CD4+ and CD8+ T cells, which are vital for long-term immunity and the control of viral infections[21,23]. Given that antibody levels tend to wane several months after the initial vaccination series, the administration of booster doses becomes critical in maintaining vaccine efficacy and providing robust protection, especially for immunocompromised individuals such as those undergoing hemodialysis[22,23]. These findings align with broader public health strategies to enhance vaccine coverage and efficacy against evolving viral threats, underscoring the necessity of booster doses in vulnerable populations to reduce the risk of severe illness and improve overall patient outcomes[22].

However, it is important to note that our study has some limitations. The sample size was relatively small due to the high cost of immunological assays, which limited the number of participants that could be included. Additionally, the cellular immune response was assessed in a limited number of participants.

In conclusion, our study provides valuable insights into the effectiveness, immunogenicity, and long-term outcomes of the Sinopharm (BBIBP-CorV) COVID-19 vaccine in HD patients compared to healthy individuals. While the vaccine can be used safely in HD patients, the impaired cellular and humoral immunity observed in this population necessitates adjustments in vaccination strategies. The robust humoral immune response elicited by the Sinopharm vaccine suggests that this vaccine is effective in inducing a protective immune response in HD patients. Moreover, the significant differences observed between various time points post-vaccination indicate that the immune response continues to evolve and strengthen over time, potentially providing long-lasting protection against SARS-CoV-2 infection. The significant correlations between humoral and cellular immunity in patients who received a third vaccine dose highlight the potential benefit of additional doses in maintaining optimal protection in this vulnerable population.

Based on our findings, we recommend that guidelines for COVID-19 vaccination in HD patients should consider the inclusion of booster doses to maintain and enhance the coordination between humoral and cellular immune responses over time. Further research is needed to confirm these findings in larger cohorts, to determine the optimal timing and dosage of booster doses for HD patients, and to optimize vaccination protocols and monitor long-term immune responses in this population. Nonetheless, our results contribute to the growing body of evidence on COVID-19 vaccination in HD patients and underscore the importance of tailoring vaccination strategies to

meet the unique needs of this population in the ongoing fight against the pandemic.

Conclusion

In conclusion, this study demonstrates the efficacy of COVID-19 vaccination in HD patients, albeit with a diminished response compared to healthy individuals. While HD patients showed significant increases in antibody levels post-vaccination, the response was lower than in healthy controls, with 30% remaining unresponsive. Notably, breakthrough infection rates in HD patients were comparable to or slightly better than those in healthy controls, possibly due to stricter adherence to preventive measures and frequent healthcare interactions. However, contrary to expectations, booster doses showed minimal impact on enhancing immune responses or reducing breakthrough infections in this population. These findings underscore the complexity of vaccine responses in HD patients and highlight the need for further research into alternative strategies to improve vaccine efficacy in this vulnerable group. Future studies should explore tailored vaccination approaches, including modified dosing schedules or alternative vaccine platforms, to optimize protection against COVID-19 in HD patients, given the limited efficacy of current booster regimens.

Competing of Interest:

The authors declared no potential financial conflict of interest.

Funding Statement:

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We would like to take a moment to remember Dr. Amirzargar, whose passion for science and commitment to the advancement of knowledge left a lasting impression on all who knew him. His kindness, wisdom, and unwavering support will be deeply missed. We honor his memory and the positive influence he had on his colleagues and the broader academic community.

Author Contribution

SAAS-N contributed to conceptualization, methodology, formal analysis, and wrote the original draft. YKB assisted in writing the original draft and provided resources. AAK, MSN, and YF were involved in investigation. NF contributed to investigation and writing the original draft. AS-N performed formal analysis. MAP and SRM were responsible for conceptualization and methodology, with MAP also contributing to validation and supervision. MN provided validation. AAA contributed to methodology, validation, supervision, funding acquisition, and resources. SS played a key role in conceptualization, methodology, validation, supervision, project administration, funding acquisition, and resources, and MF-M conducted investigation and data curation.

Data Availability Statement

The code for analysis of this work is available at: https://github.com/Sdamirsa/Sinopharm_C19_Response_HemodyalsisPatients/tree/main. The data are not fully available online due to ethical committee mandate, but will be made available to researchers upon reasonable request to the corresponding author.

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Supplemantary File

This is a suppelmantary file to "**Sinopharm (BBIBP-CorV) COVID-19 Vaccination in Hemodialysis Patients and Healthy Individuals: 1-year Effectiveness and Immunogenicity**" by Seyed Amir Ahmad Safavi-Naini, Yasaman Khaili Baseri, Azadeh Ahmadi Koomleh, Niloofar Fakour, Aryan Salahi-Niri, Mahsa Saeedi Niasar, Yeganeh Farsi, Mohamad Amin Pourhoseingholi, Seyed Reza Mohebbi, Mohsen Nafar, Ali Akbar Amirzargar, Shiva Samavat, Marieh Farrokhy-Moghaddam.

Supplementary Table S1. Information of kits used in this study.

Kit Name	Description	Ranges	Sensitivity	Specificity	
Elecsys® Anti-SARS-CoV-2	Immunoassay for the qualitative detection of antibodies (including IgG) against SARS-CoV-2		85.3 % (7-14 days)	99.8%	https://diagnostics.roche.com/global/en/products/params/elecsys-anti-sars-cov-2.html
Quanti SARS-CoV-2 Anti-Spike IgG ELISA Kit	Enzyme Immunoassay for the Quantitative detection of anti-Spike IgG in Human Serum		98.16%	99.1%	https://pishtazteb.com/en/wp-content/uploads/2022/01/Quanti-SARS-CoV-2-Anti-Spike-IgG-IFU-Eng-29-1-400-003.pdf
Quanti SARS-CoV-2 Anti-RBD IgG ELISA Kit	Enzyme Immunoassay for the Quantitative detection of anti-Spike IgG in Human Serum	<5 RU/ml: Negative; ≥5 RU/ml: Positive	97.1%	100%	https://pishtazteb.com/en/wp-content/uploads/2022/01/Quanti-SARS-CoV-2-Anti-RBD-IgG-IFU-Eng-V1.pdf
SARS-CoV-2 Neutralizing Antibody ELISA Kit	Enzyme Immunoassay for the detection of total neutralizing antibodies to SARS-CoV-2 in human serum		94.1 %	98.3%	https://pishtazteb.com/en/wp-content/uploads/2022/01/SARS-CoV-2-Neut-Ab-IFU-Eng-29-1-400.pdf
EUROIMMUN SARS-CoV-2 Quan-T-Cell IGRA	The Quan-T-Cell ELISA provides in vitro determination of interferon gamma in human heparinised plasma.		-	-	https://www.euroimmun.de/fileadmin/Subsidiaries/Japan/Documents/IFU/IFU_EQ_6841-9601.pdf

Supplementary Table S2. Adverse reactions after vaccination in hemodialysis cases and healthy controls.

	Total	HD Patients	Healthy Control	P-value
	Percent (event/population)	Percent (event/population)	Percent (event/population)	
Adverse Event after D1				
No	83.62% (97 / 116)	78.16% (N= 68 / 87)	100.0% (N= 29 / 29)	0.014
Yes	16.38% (19 / 116)	21.84% (N= 19 / 87)		0.014
Injection site D1 (pain)				
No	88.79% (103 / 116)	88.51% (N= 77 / 87)	89.66% (N= 26 / 29)	1
Yes	11.21% (13 / 116)	11.49% (N= 10 / 87)	10.34% (N= 3 / 29)	1
Injection site D1 (swelling)				
No	99.14% (115 / 116)	98.85% (N= 86 / 87)	100.0% (N= 29 / 29)	1
Yes	0.86% (1 / 116)	1.15% (N= 1 / 87)		1
Systemic reaction D1 (malaise)				
No	94.83% (110 / 116)	95.4% (N= 83 / 87)	93.1% (N= 27 / 29)	1
Yes	5.17% (6 / 116)	4.6% (N= 4 / 87)	6.9% (N= 2 / 29)	1
Systemic reaction D1 (headache)				
No	97.41% (113 / 116)	98.85% (N= 86 / 87)	93.1% (N= 27 / 29)	0.311
Yes	2.59% (3 / 116)	1.15% (N= 1 / 87)	6.9% (N= 2 / 29)	0.311

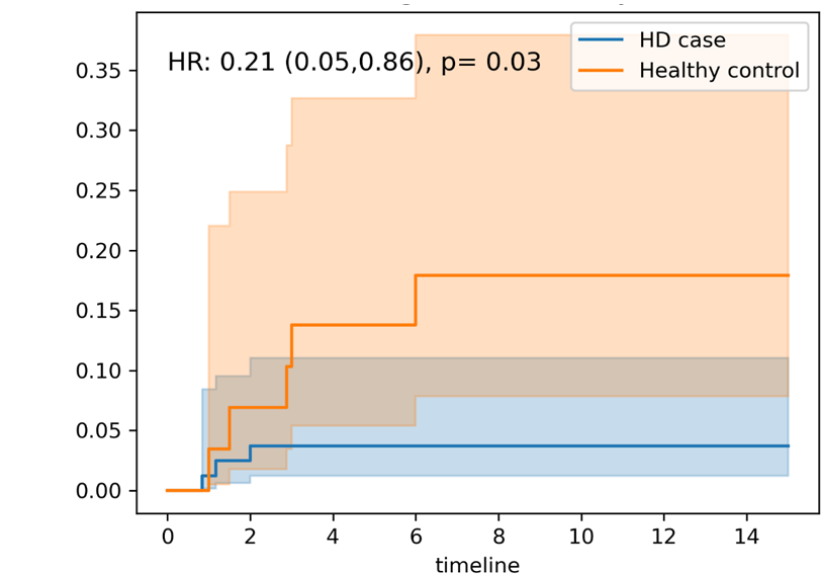
	Total	HD Patients	Healthy Control	P-value
Systemic reaction D1 (fever)				
No	91.38% (106 / 116)	89.66% (N= 78 / 87)	96.55% (N= 28 / 29)	0.445
Yes	8.62% (10 / 116)	10.34% (N= 9 / 87)	3.45% (N= 1 / 29)	0.445
Anaphylaxis D1				
No	100.0% (116 / 116)	100.0% (N= 87 / 87)	100.0% (N= 29 / 29)	1
Grade of reaction D1 (Mild: self-resolving, Moderate: relive with treatment, Severe: prevent daily activity)				
No Reaction	82.76% (96 / 116)	77.01% (N= 67 / 87)	100.0% (N= 29 / 29)	0.018
Mild	10.34% (12 / 116)	13.79% (N= 12 / 87)		0.018
Moderate	6.9% (8 / 116)	9.2% (N= 8 / 87)		0.018
Adverse event after D2				
No	90.52% (105 / 116)	87.36% (N= 76 / 87)	100.0% (N= 29 / 29)	0.1
Yes	9.48% (11 / 116)	12.64% (N= 11 / 87)		0.1
Injection site D2 (pain/swelling)				
No	92.24% (107 / 116)	91.95% (N= 80 / 87)	93.1% (N= 27 / 29)	1
Yes	7.76% (9 / 116)	8.05% (N= 7 / 87)	6.9% (N= 2 / 29)	1
Systemic reaction D2 (malaise)				
No	97.41% (113 / 116)	96.55% (N= 84 / 87)	100.0% (N= 29 / 29)	0.736
Yes	2.59% (3 / 116)	3.45% (N= 3 / 87)		0.736
Systemic reaction D2 (headache)				
No	96.55% (112 / 116)	98.85% (N= 86 / 87)	89.66% (N= 26 / 29)	0.078
Yes	3.45% (4 / 116)	1.15% (N= 1 / 87)	10.34% (N= 3 / 29)	0.078
Systemic reaction D2 (fever)				
No	96.55% (112 / 116)	95.4% (N= 83 / 87)	100.0% (N= 29 / 29)	0.557
Yes	3.45% (4 / 116)	4.6% (N= 4 / 87)		0.557
Systemic reaction D2 (extremities pain)				
No	98.28% (114 / 116)	98.85% (N= 86 / 87)	96.55% (N= 28 / 29)	1
Yes	1.72% (2 / 116)	1.15% (N= 1 / 87)	3.45% (N= 1 / 29)	1
Anaphylaxis D2				
No	100.0% (116 / 116)	100.0% (N= 87 / 87)	100.0% (N= 29 / 29)	1
Grade of reaction D2 (Mild: self-resolving, Moderate: relive with treatment, Severe: prevent daily activity)				
No Reaction	89.66% (104 / 116)	86.21% (N= 75 / 87)	100.0% (N= 29 / 29)	0.107
Moderate	6.03% (7 / 116)	8.05% (N= 7 / 87)		0.107
Mild	4.31% (5 / 116)	5.75% (N= 5 / 87)		0.107
Hospitalization due to vaccination D2				
No	100.0% (116 / 116)	100.0% (N= 87 / 87)	100.0% (N= 29 / 29)	1

Supplementary Table S3. COVDI-19 infection during immunization window or 21 days after D2 in hemodialysis patients and healthy controls.

	Total	HD Patients	Healthy Control	P-value
	Percent (event/population)	Percent (event/population)	Percent (event/population)	
COVID-19 Infection during Immunization Window				
No	94.83% (110 / 116)	93.1% (N= 81 / 87)	100.0% (N= 29 / 29)	0.333
Yes	5.17% (6 / 116)	6.9% (N= 6 / 87)		0.333
Diagnosis Method				
PCR	66.67% (4 / 6)	66.67% (N= 4 / 6)		1
CT	33.33% (2 / 6)	33.33% (N= 2 / 6)		1
Management setting				

	Total	HD Patients	Healthy Control	P-value
Ward	66.67% (4 / 6)	66.67% (N= 4 / 6)		1
ICU	33.33% (2 / 6)	33.33% (N= 2 / 6)		1
COVID-19 infection after Immunization (Breakthrough Infection)				
No	91.38% (106 / 116)	94.25% (N= 82 / 87)	82.76% (N= 24 / 29)	0.127
Yes	8.62% (10 / 116)	5.75% (N= 5 / 87)	17.24% (N= 5 / 29)	0.127
Diagnosis Method				
PCR	70.0% (7 / 10)	60.0% (N= 3 / 5)	80.0% (N= 4 / 5)	0.208
clinical	20.0% (2 / 10)	40.0% (N= 2 / 5)		0.208
CT	10.0% (1 / 10)		20.0% (N= 1 / 5)	0.208
Infection interval (Days)	84.66±59.06 (N= 11)	83.33±65.09 (N= 6)	86.25±58.46 (N= 5)	
Management setting				
Home	80.0% (8 / 10)	80.0% (N= 4 / 5)	80.0% (N= 4 / 5)	1
Ward	20.0% (2 / 10)	20.0% (N= 1 / 5)	20.0% (N= 1 / 5)	1
D3 Administration	5.95±0.83 (N= 60)	6.04±0.81 (N= 50)	5.5±0.85 (N= 10)	
Vaccine Type				
Sinopharm	75.93% (41 / 54)	97.62% (N= 41 / 42)		0
AstraZeneca	22.22% (12 / 54)		100.0% (N= 12 / 12)	0
Pastococ	1.85% (1 / 54)	2.38% (N= 1 / 42)		0
Follow-up period (months from D2 to second call)	13.46±0.81 (N= 114)	13.32±0.8 (N= 85)	13.9±0.67 (N= 29)	

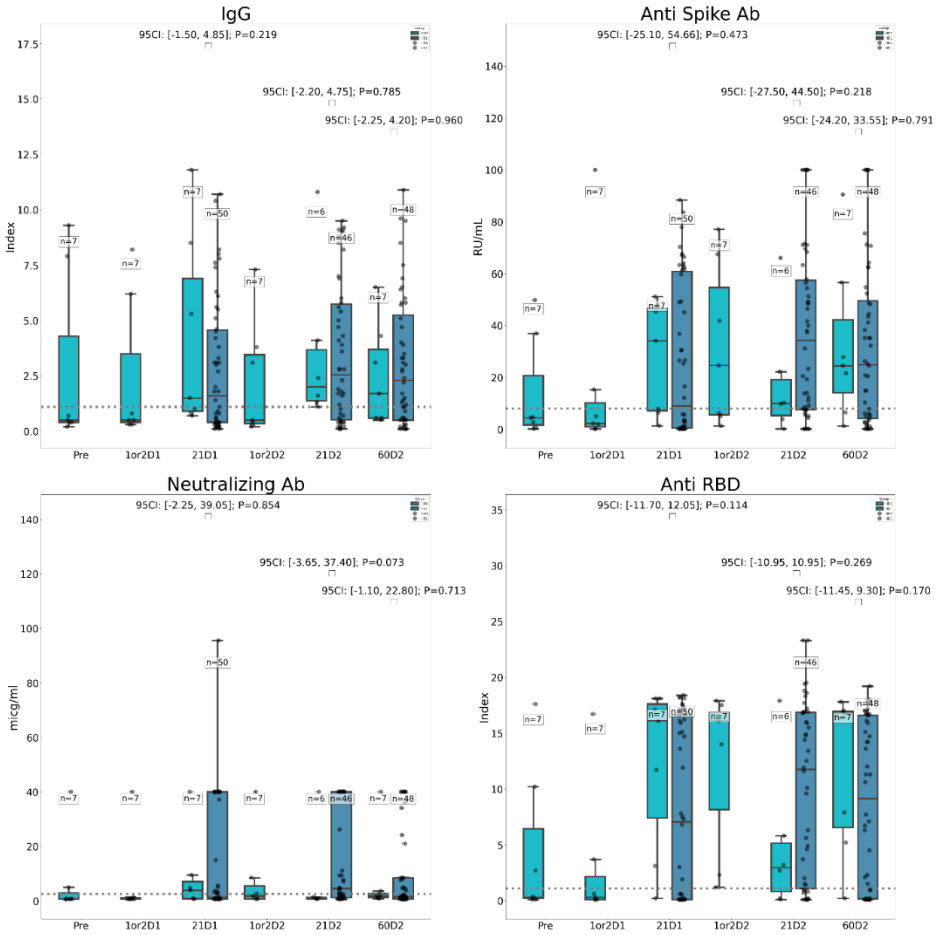
Supplemantary Figure S1. Cumulative density plot illustrating the chance of breakthrough infection in hemodialysis cases and healthy controls, along with its hazard ratio (HR) considering HD cases as the reference.



HD case								
At risk	86	78	75	43	30	30	26	1
Censored	1	6	9	41	54	54	58	83
Events	0	3	3	3	3	3	3	3
Healthy control								
At risk	29	27	24	18	18	18	18	1
Censored	0	0	1	6	6	6	6	23
Events	0	2	4	5	5	5	5	5

Footnote: The administration of the third dose and the last follow-up were treated as censoring events, while breakthrough infections were considered as events. In contrast to Figure 2, cases were confirmed only by clinical symptom and PCR test (excluding two patients confirmed by symptom only). The proportional hazards assumption was, assessed through the Scaled Schoenfeld Residual Test and a significance level of 0.05 for the p-value.

Supplementary Figure S2. Immunogenicity in HD0 and HD1 cohorts



Supplementary Figure S3. Immunogenicity of HD vs healthy control in a cohort with previous COVID-19 infection