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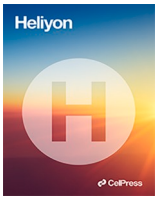

Research article

Increase in HIV reservoir and T cell immune response after CoronaVac vaccination in people living with HIV

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ABSTRACT

Introduction: CoronaVac, an inactivated vaccine developed by Sinovac Life Sciences, has been widely used for protection against Coronavirus Disease 2019 (COVID-19). This study investigates its effect on the HIV reservoir and T cell repertoires in people living with HIV (PLWHs).

Methods: Blood samples were collected from fifteen PLWHs who were administered at least two doses of CoronaVac between April 2021 and February 2022. The levels of cell-associated HIV RNA (CA HIV RNA) and HIV DNA, as well as the T cell receptor (TCR) repertoire profiles, TCR clustering and TCRβ annotation, were studied.

Results: A significant increase was observed in CA HIV RNA at 2 weeks (431.5 ± 164.2 copies/10^6 cells, $P = 0.039$) and 12 weeks (330.2 ± 105.9 copies/10^6 cells, $P = 0.019$) after the second dose, when compared to the baseline (0 weeks) (73.6 ± 23.7 copies/10^6 cells). Various diversity indices of the TCRβ repertoire, including Shannon index, Pielou's evenness index, and Hvj Index, revealed a slight increase ($P < 0.05$) following CoronaVac vaccination. The proportion of overlapping TCRβ clonotypes increased from baseline (31.9 %) to 2 weeks (32.5 %) and 12 weeks (40.4 %) after the second dose. We also found that the breadth and depth of COVID-19-specific T cells increased from baseline (0.003 and 0.0035) to 12 weeks (0.0066 and 0.0058) post the second dose.

Conclusions: Our study demonstrated an initial increase in HIV reservoir and TCR repertoire diversity, as well as an expansion in the depth and breadth of COVID-19-specific T-cell clones among CoronaVac-vaccinated PLWHs. These findings provide important insights into the effects of COVID-19 vaccination in PLWHs.

1. Introduction

The Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected millions of individuals worldwide. People living with HIV (PLWH) are at an elevated risk of experiencing severe symptoms and mortality if infected with COVID-19 [1]. Extensive researches indicated that poor outcomes among PLWHs are closely associated with comorbidities and a low $CD4^+$ T cell count, rather than solely the result of an HIV diagnosis [2]. This suggests that immune deficiency is a major risk factor for severe COVID-19 development in PLWHs. Hence, vaccination is crucial for the protection of this

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vulnerable population against SARS-CoV-2 infection and severe COVID-19 disease.

The immune response to the COVID-19 vaccine involves B-cell-mediated humoral responses through antibodies and T-cell-mediated responses [3]. $CD4^+$ T cells play a vital role in supporting neutralizing antibody responses and persistent antibody responses, along with the generation of affinity-matured memory B cells [4]. Additionally, $CD4^+$ T cells support the immune response of $CD8^+$ T cells, promoting the development of long-term memory $CD8^+$ T cells, which enhances antiviral capabilities [5]. Clinical studies have emphasized the importance of SARS-CoV-2-specific $CD8^+$ cytotoxic T lymphocytes and memory cells in patients recovering from COVID-19 [6,7]. T cells use hypervariable T-cell receptors (TCR) to recognize pathogen-derived peptides presented on the cell surface by major histocompatibility complex (MHC).

An assessment of the efficacy of COVID-19 vaccine relies on the diversity of TCR repertoire, which measures the range of foreign antigens [8]. Therefore, evaluating the TCR repertoire responses is a vital step in assessing the impact of CoronaVac, an inactivated SARS-CoV-2 vaccine developed by Sinovac. CoronaVac has been widely administered and has demonstrated significant effectiveness in preventing hospitalizations, ICU admissions, and deaths caused by SARS-CoV-2 [9]. However, few studies evaluated TCR repertoire responses to CoronaVac in the PLWH population.

Previous studies have demonstrated that vaccination can temporarily activate the immune system, thereby leading to increased levels of HIV RNA in both cell-free and cell-associated (CA HIV RNA) forms [10–12]. However, a recent study reported a decrease in CA HIV RNA after the administration of the SARS-CoV-2 mRNA vaccine BNT162b2 in PLWH with suppressed viral load [13]. Another research group showed that, except for older PLWHs with low-level viremia, the size of the HIV reservoir remained stable in PLWHs who received COVID-19 vaccines, including mRNA and adenovirus-vectored vaccines [14]. Nevertheless, the influence of vaccination on the HIV reservoir in the context of CoronaVac has not yet been fully explored.

In the present study, we recruited PLWHs to receive CoronaVac, in order to gain a deeper understanding of the immune responses induced by this vaccine. Our aim was to investigate the effect of CoronaVac on the HIV reservoir and T cell repertoires in PLWHs.

2. Methods

2.1. Participants and study design

This study enrolled a total of 15 participants between April and August 2021. Table 1 presents the clinical characteristics of the participants. This study received approval from the institutional review boards of the First Affiliated Hospital, School of Medicine, Zhejiang University (Reference Number: 2021376). Each participant provided written informed consent for the publication of their case details and any accompanying images. This study adhered to the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association.

The inclusion criteria for this study were as follows: male individuals aged between 18 and 65, HIV-positive with at least one year of antiretroviral therapy (ART), and a willingness to receive a minimum of two doses of CoronaVac. Participants with severe chronic diseases or acute conditions were excluded. All participants were assessed through a questionnaire before and during the study to confirm no history or current infection of SARS-CoV-2.

2.2. Sample collection

Baseline blood samples were collected from participants prior to vaccination, as well as at 2 weeks and 12 weeks after the second dose of CoronaVac (Fig. 1A). Plasma and peripheral blood mononuclear cells (PBMC) were isolated and subsequently stored at −80 °C and in liquid nitrogen, respectively. Partial blood samples were collected at two weeks after the third dose of CoronaVac. The HIV plasma viral load (VL) was quantified using the Abbott Real Time HIV-1 assay (Abbott Laboratories, Abbott Park, Illinois, USA), with a lower limit of detection set at 20 copies/mL. $CD4^+$ and $CD8^+$ T-cell counts were analyzed using 4-colour flow cytometry.

Table 1
Clinical characteristics of the fifteen participants.

ID	Age	Gender	HIV diagnosis	HIV RNA (copies/ml)	$CD4^+$ T cells (cells/μL)	Antiretroviral therapy
A003	43	Male	2016	under the detection limit	243	TAF + FTC + EVG/c
A004	32	Male	2017	under the detection limit	601	TAF + FTC + BIC
A005	28	Male	2018	under the detection limit	902	TAF + FTC + BIC
A006	34	Male	2018	under the detection limit	225	TAF + FTC + DTG
A008	30	Male	2015	under the detection limit	612	3 TC + DTG
A010	34	Male	2020	under the detection limit	252	TAF + FTC + BIC
A011	30	Male	2018	under the detection limit	263	3 TC + ABC + DTG
A012	39	Male	2008	under the detection limit	415	TAF + FTC + EVG/c
A013	54	Male	2012	under the detection limit	352	TAF + FTC + BIC
A014	26	Male	2020	under the detection limit	832	FTC + TDF + DTG
A017	26	Male	2018	under the detection limit	628	TAF + FTC + EVG/c
A019	56	Male	2016	under the detection limit	316	TAF + FTC + BIC
A021	20	Male	2020	under the detection limit	473	TAF + FTC + BIC
A022	23	Male	2020	under the detection limit	485	TAF + FTC + EVG/c
A023	51	Male	2017	under the detection limit	190	TAF + FTC + EVG/c

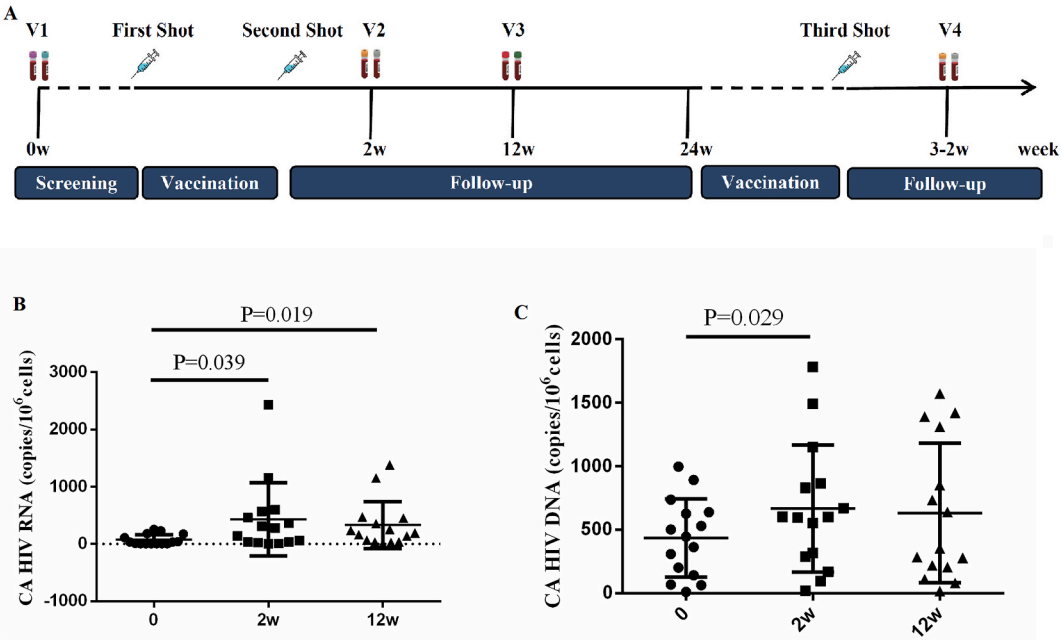

Fig. 1. The Impact of CoronaVac Vaccination on the HIV Reservoir (A) Study design and Sample collection. Baseline blood samples were collected at baseline, 2 weeks and 12 weeks after the second vaccination, as well as 2 weeks after the third vaccination. There was a significant increase in cell-associated HIV RNA (B) and HIV DNA (C) following the administration of two doses of CoronaVac.

2.3. HIV reservoir quantification

The concentration of CA HIV RNA was measured using the HIV-1 RT-PCR Assay V2 (Qiagen, Hilden, Germany). The SUPBIO HIV Quantitative Detection Kit (SUPBIO, Guangzhou, China) was used to amplify and quantify HIV DNA in PBMC for the LTR gene, using a fluorescence-based, real-time method.

2.4. Bulk cell TCR sequencing and analysis

RNA extraction was performed from approximately 1×10^7 thawed PBMCs using the RNeasy Plus Mini Kit (Qiagen, Germany), following the manufacturer's protocol. Subsequently, the extracted RNA samples underwent next generation sequencing (NGS) for profiling the T-cell receptor beta locus (TRBs) using the ImmuHub® TCR profiling system (ImmuQuad Biotech, Hangzhou, China). Briefly, a 5′ rapid amplification of cDNA ends (RACE) unbiased amplification protocol was utilized, incorporating unique molecular identifiers (UMIs) to control bottlenecks, correct PCR and sequencing errors, and remove duplicates [15]. Sequencing was carried out on an Illumina NovaSeq® system with PE150 mode.

The resulting raw sequence reads, each tagged with a UMI, were used to map V, D, J and C segments with NCBI human VDJdb database [16]. The complementarity-determining region 3 (CDR3) regions were extracted, and clonotypes were assembled for all clones. The sequences with out-of-frame stop codons were eliminated from the identified TCRβ repertoire. Nucleotide and amino acid sequences of CDR3 in TCRβ were determined. VDJtools was employed for further analysis of the TCR clonotype data [17].

2.5. Clustering estimation of TRB clonotypes

We utilized the GLIPH2 (grouping of lymphocyte interactions with paratope hotspots version 2) algorithm to analyze the TRB repertoire of all patients and identify clonal groupings with identical or similar antigen specificities [18]. A reference TCRβ dataset of combined naïve $CD4^+$ and $CD8^+$ repertoires was adopted, using the default parameters (http://50.255.35.37:8080/). The GLIPH2 analysis identified TCRβ clusters based on CDR3 sequence similarity (Hamming distance of CDR3 sequences of the same length). These clusters were categorized as global or motif-based and exhibited motif enrichment in TCRβ clonotypes.

2.6. Clonal breadth and depth of COVID-19-specific T cells

To annotate reactive TCRs with potential antigen specificities against SARS-CoV-2 epitopes, we compared TRBV gene segments to known COVID-19-specifc clonotypes in the VDJdb database. To evaluate the clonal breadth and depth of the COVID-19-specific TCRs after vaccination, we quantified their number and/or frequency in each group. Clonal breadth represents the proportion of distinct TCRs that are specific to COVID-19. It is calculated by dividing the number of unique COVID-19-specific TCRs by the total number of

unique TCRs in the entire repertoire. Clonal depth, on the other hand, refers to the cumulative frequency of COVID-19-specific TCRs in the repertoire. It is calculated by dividing the total number of COVID-19-specific TCRs by the total number of TCRs in the entire repertoire.

2.7. Statistical analysis

The data was summarized using descriptive statistics. Normally distributed data was reported as mean ± standard deviation, while skewed distribution data was reported as median (25th to 75th quantiles). Statistical significance was evaluated using a two-tailed Student's t-test and one-way ANOVA analysis. These tests were conducted with GraphPad Prism version 5.02 (GraphPad Software, Inc., San Diego, CA). A significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Participant characteristics

A total of 15 PLWHs were enrolled in this study. The participants were male and had a median age of 32 years (IQR: 27–41). At the time of their recruitment for the study, the participants' median CD4 count was 415/μl (IQR: 257.5–606.5). Throughout the follow-up period, their HIV viral loads remained below the lower detection limit (20 copies/mL), thereby indicating sustained virological suppression. Detailed clinical characteristics of these participants are presented in Table 1.

3.2. Increase in the HIV reservoirs after CoronaVac vaccination

Following two doses of CoronaVac, a significant increase was observed in CA HIV RNA at 2 weeks (431.5 ± 635.9 copies/10^6 cells, $P = 0.039$) and 12 weeks (330.2 ± 409.9 copies/10^6 cells, $P = 0.019$), when compared to the baseline (0 weeks) (73.6 ± 91.8 copies/

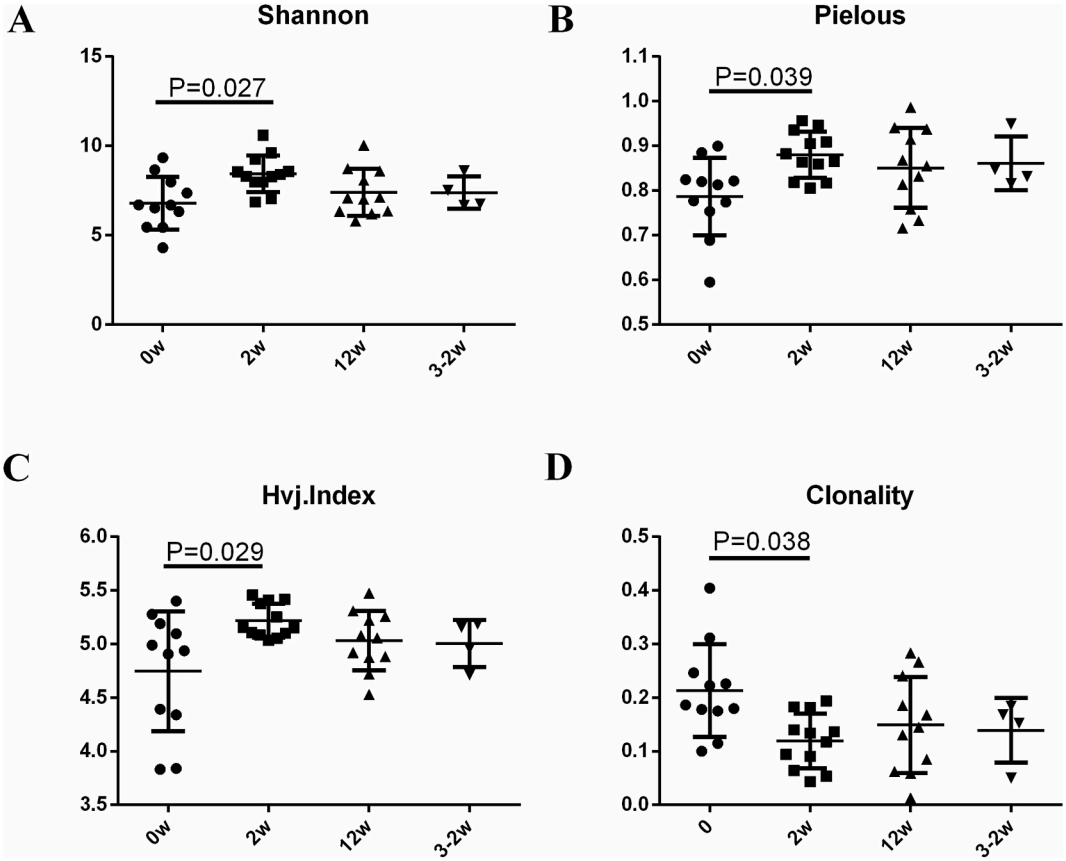

Fig. 2. Differences in TCRβ Repertoire Diversities and Clonalities after CoronaVac Vaccination.
Various diversity indices, such as the Shannon index (A), Pielou's evenness index (B), and Hvj Index (C), were employed. The analyses demonstrated a slight increase in TCRβ repertoire diversity after CoronaVac vaccination. Additionally, a significant decrease in clonality (D) was observed following CoronaVac vaccination.

10^6 cells) (Fig. 1B). Similarly, CA HIV DNA showed a significant increase from baseline (435.7 ± 307.3 copies/10^6 cells) to 2 weeks (668.6 ± 499.8 copies/10^6 cells, P = 0.029) and 12 weeks (631.3 ± 549.0 copies/10^6 cells, P = 0.14) after the administration of the second dose (Fig. 1C).

3.3. Increase in TCRβ Repertoire Diversities after CoronaVac vaccination

Due to the sample availability, we performed bulk TCR sequencing on 11 baseline samples, 12 samples at 2 weeks, 11 samples at 12 weeks and 4 samples in 2 weeks after the third dose. Based on the observed differences in the HIV reservoirs, we subsequently investigated the characteristics of the TCRβ repertoire after CoronaVac vaccination using various diversity indices, including Shannon index, Pielou's evenness index, and Hvj Index. These analyses revealed a slight increase (P < 0.05) in TCRβ repertoire diversity following CoronaVac vaccination (Fig. 2A–C). These findings suggested that CoronaVac vaccination may enhance the diversity of

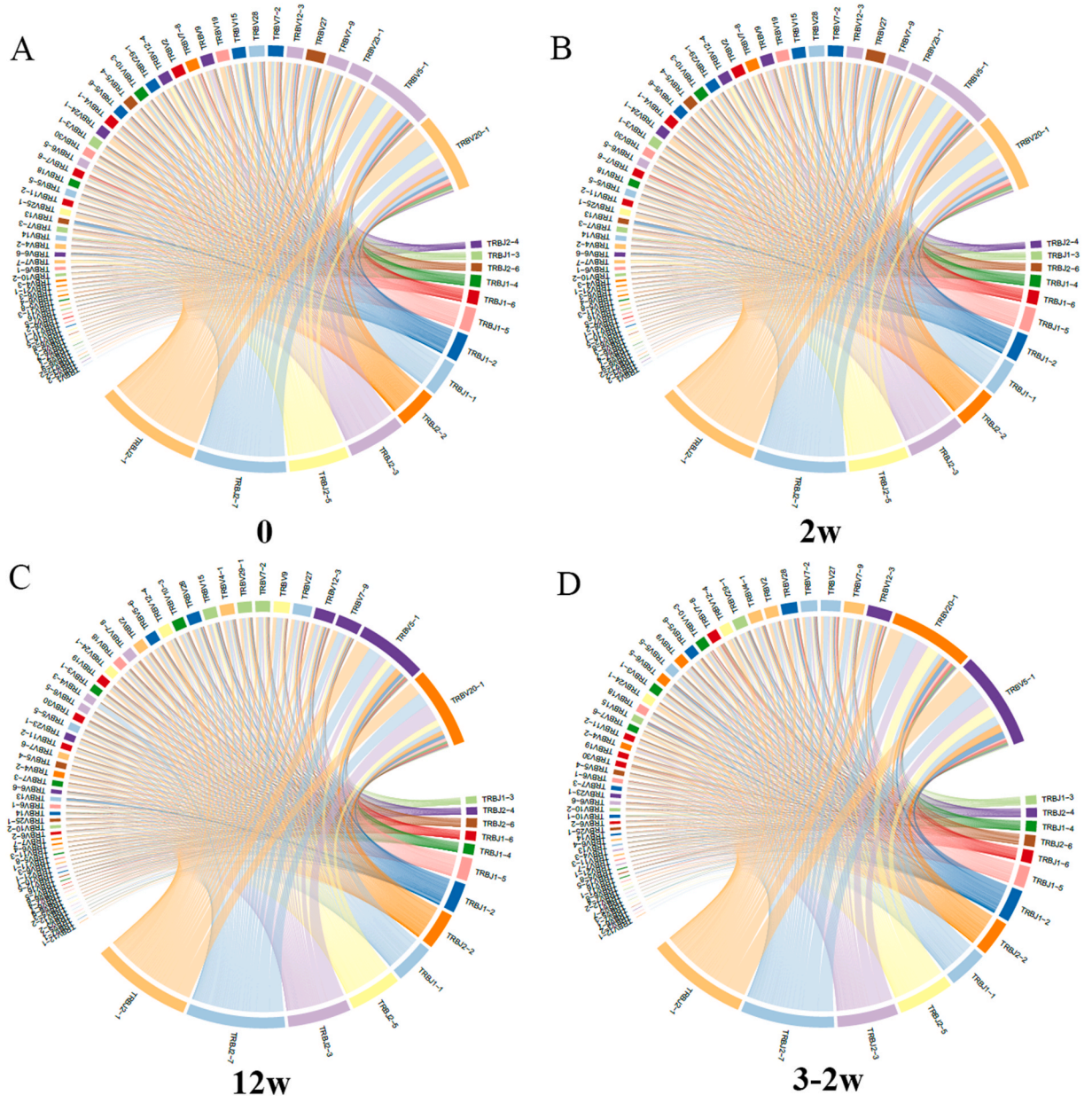

Fig. 3. Expression of V-J Paired Genes after CoronaVac Vaccination using Circos Figures.
Each color block represents a gene segment, and the width of the block represents its frequency. A certain clonal expansion of VJ gene segments, namely TRBJ2-1, TRBJ2-7, TRBV20-1, and TRBV5-1, was observed at baseline (A), 2 weeks (B), and 12 weeks (C) after the second vaccination, as well as 2 weeks (D) after the third vaccination.

peripheral T cell repertoires, when compared to unvaccinated individuals. Furthermore, clonality was independently estimated for each sample and showed a significant decrease after the second dose of vaccine (Fig. 2D).

3.4. Analysis of V and J gene segments

We performed an in-depth analysis of the expression of VJ paired genes among different groups using Circos figures. The analysis revealed clonal expansion of VJ gene segments, including TRBJ2-1, TRBJ2-7, TRBV20-1 and TRBV5-1 (Fig. 3A–D). The preferential recombination usage of V(D)J gene segments before vaccination (TRBJ2-1-TRBV20-1, frequency: 0.033) (Fig. 3A) and after the second dose (TRBJ2-3-TRBV20-1, frequencies: 0.038 at 2 weeks, 0.052 at 12 weeks) (Fig. 3B–C) showed considerable differences. Following the third vaccination, the preferential recombination usage shifted to TRBJ2-1-TRBV5-1 (frequency: 0.041) (Fig. 3D).

3.5. Clonotype tracking

A total of 153,409 unique clonotypes (Fig. 4A), detected across 38 samples, were tracked to observe their proportions in each group, thereby illustrating the changes in the immune repertoire at different stages of vaccination (Fig. 4B). The sum proportion of overlapped clonotypes increased from baseline (31.9 %) to 2 weeks (32.5 %) and 12 weeks (40.4 %) after the administration of two doses of CoronaVac.

There were notable differences in the proportion of certain sequences in vaccinated samples, including CASSRASGDRLEQYF,

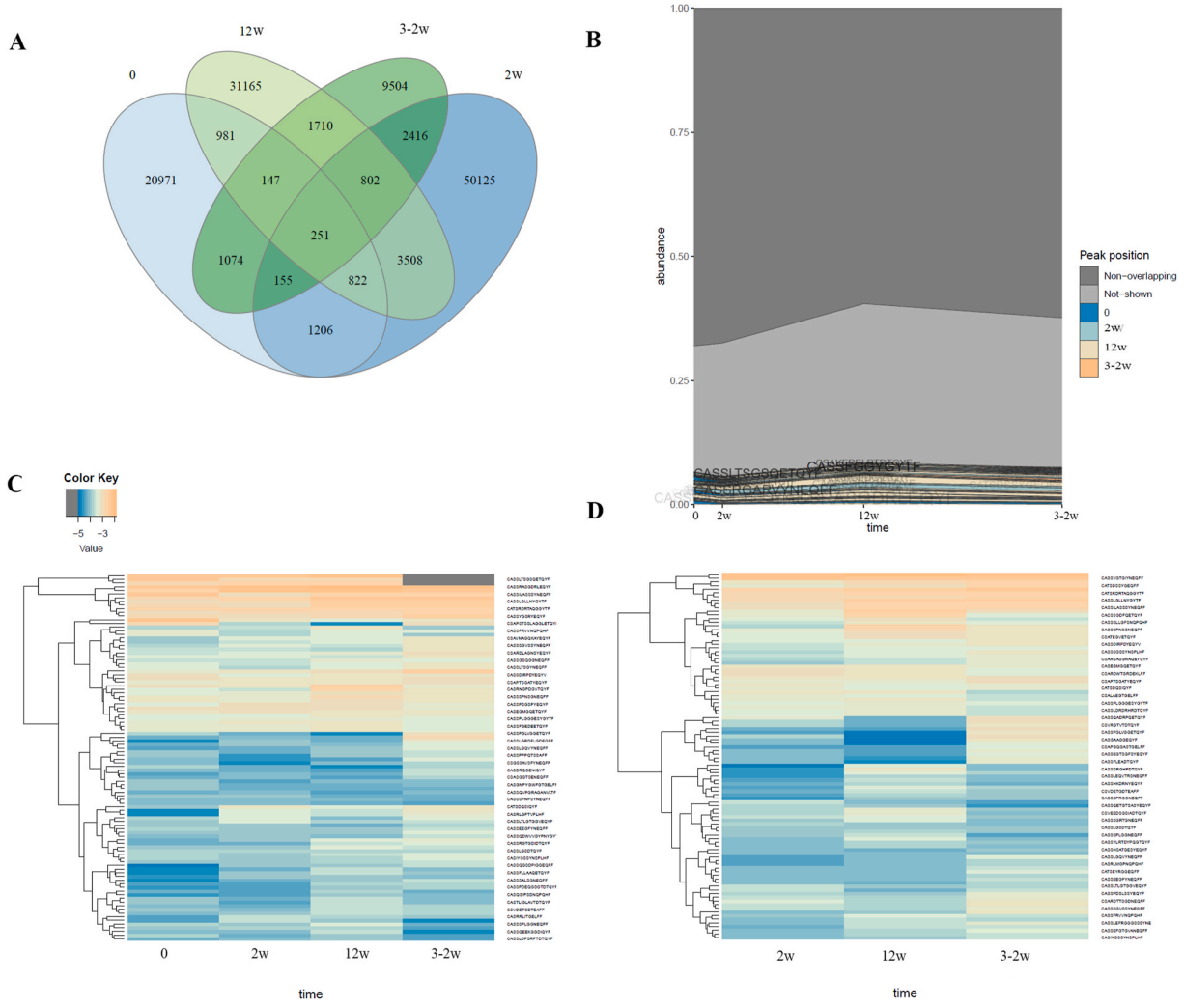

Fig. 4. Clonotype Tracking (A) The Venn diagram illustrates the numbers of common and unique clonotypes before and after vaccination. (B) Abundance plot of clonotypes. The stacked abundance of the top 100 clonotypes is displayed at different time points. These clonotypes were tracked to observe their proportions during various stages of vaccination. (C, D) Heatmap for clonotype tracking. The heatmap depicts the abundances of the top 100 joint clonotypes at different time points.

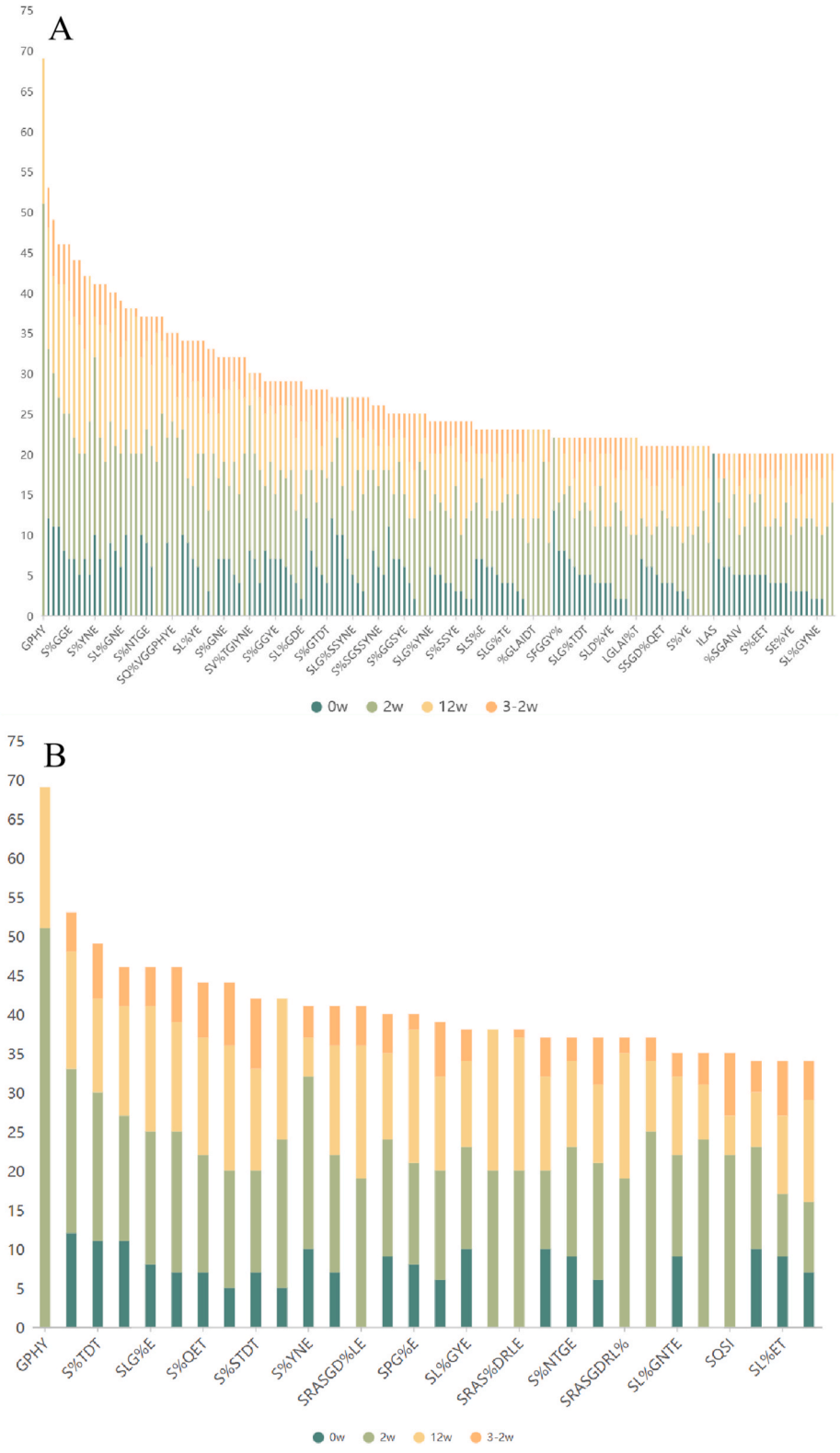

Fig. 5. Divergent Characteristics of TCRβ Clusters After CoronaVac Vaccination
The TCRβ clusters identified by GLIPH2 were displayed in stacked bar chart (A). The TCRβ clusters were visualized using a stacked bar chart. Each bar represents a cluster, and the height of each segment within the bar corresponds to the number of unique TCRβ clonotypes in that cluster. Different colors represent different time points. Top 30 Clusters were specifically highlighted in the stacked bar chart (B).

CASSVGTGIYNEQFF, CASSLVGTGLTGANVLTF, and CASSLGLLNYGYTF, which were 2–3 times more abundant. Conversely, the proportion of CASSILASSSYNEQFF and CASSRGARVYNEQFF decreased in samples after vaccination (Fig. 4C-D). These findings suggest a potential association between these high-abundance clonotypes and the CoronaVac vaccination.

3.6. Divergent Characteristics of TRB clusters after CoronaVac vaccination

To identify the potential function of TRB in CoronaVac vaccination, we analyzed the TRB clusters (Fig. 5A) and identified the top 30 clusters evaluated by GLIPH2 (Fig. 5B). Some clusters had a 2–3 times higher proportion in vaccinated samples, including S%SYE, S% TDT, SLGG%E, and SLG%E. New clusters, including GPHY and SRASGD%LE, emerged after vaccination (Fig. 5B).

3.7. Increased clonal breadth and depth of COVID-19-specific TCR

To gain a better understanding of the immune responses following vaccination, we evaluated TCR sequences based on the specific open reading frame (ORF) of the COVID-19 genome. Following two doses of CoronaVac, the breadth (measured by the number of unique TCR rearrangements associated with COVID-19) (Fig. 6A) and depth (represented by the cumulative frequency of COVID-19-specific TCRs) (Fig. 6B) of COVID-19-specific TCR showed an increase from baseline (0.003 and 0.0035) to 12 weeks (0.0066 and 0.0058). Notably, after vaccination, there was higher breadth and depth of TCR specific to the spike protein (0.0041 and 0.0035), when compared to other regions associated with the surface glycoprotein.

4. Discussion

In our study, a transient increase in CA HIV RNA, HIV DNA and TCR repertoire diversity after CoronaVac vaccination was observed in PLWHs. Our study also revealed the presence of significant differences in certain TRB amino acid clonotypes and clusters of the immune repertoire after vaccination. In particular, our study showed an expansion in the depth and breadth of COVID-19-specific T-cell clones.

In this study, we observed a significant increase in the levels of CA HIV RNA and HIV DNA, which serve as markers of HIV persistence, following the administration of two doses of CoronaVac. However, our findings differ from those of the previous studies on COVID-19 vaccines. In a recent study, it was observed that 13 PLWHs who were receiving ART with suppressed viremia experienced a significant reduction in CA HIV RNA levels and an augmentation of HIV Nef-specific T cell responses, following the administration of two doses of mRNA COVID-19 vaccine BNT162b2. The same study also indicated that BNT162b2 could activate HIV transcription *ex vivo* through the RIG-I/TLR–TNF–NF κB pathway [13]. However, no measurable changes were observed in intact proviral DNA in another study on mRNA and adenovirus-vectored vaccines [14]. It is crucial to highlight that the overall levels of HIV DNA do not accurately reflect the HIV reservoir due to a substantial proportion of integrated viral genomes being defective [19]. Vaccines might merely augment the clonal populations of cells that produce defective virions. The variation in findings could also be credited to the use of different vaccine types, as evidenced by the association between an inactivated influenza vaccine and an elevated HIV proviral burden [10].

In the present study, we applied ultra-deep NGS to identify COVID-19 vaccine-specific T-cell clones in PLWHs. Our results suggest that PLWHs exhibit strong and persistent T-cell responses with significant TCR clonal expansion following vaccination, as indicated by the slight increase in repertoire diversity. During V(D)J recombination, the CDR3 region undergoes frequent random nucleotide deletions and insertions, which are vital for antigen binding. Although our study did not find any variations in the immune repertoire concerning V genes, D genes, J genes, V - J combinations, or V - D - J combinations, we did observe notable distinctions in specific clonotypes and clusters within the immune repertoire after vaccination. We employed TCR clustering, annotation, and classification methodologies to identify groups of TCRβ clonotypes that are expected to share high similarity in antigen specificity. After vaccination, there were expansions observed in certain overlapped TCRβ amino acid sequences and clusters within the immune repertoire. Further validation is necessary for the utilization of these distinctive T cell sequences in COVID-19 patients. Additionally, investigating T cells that specifically respond to SARS-CoV-2 epitopes should be a focus of future studies. Consequently, our TCR data has the potential to offer insights into a commonly observed clonal T cell phenotype within the PLWHs, thus aiding in the understanding of individual anti-SARS-CoV-2 immunity.

Our TCR sequencing analysis showed an increase in the breadth and depth of T-cell responses to multiple SARS-CoV-2 protein epitope. These findings align with the responses observed following mRNA vaccines and adenovirus-vectored vaccines [20,21]. Evaluating T-cell breadth facilitates the quantification of T-cell diversity and the strength of the T-cell immune response post-vaccination. Earlier studies employing this methodology have shown that vaccinated individuals exhibit greater breadth of spike-specific TCRs compared to those receiving a placebo, while no notable differences were observed in the breadth of non-spike TCRs [20,21]. Given the ongoing accumulation of mutations in the SARS-CoV-2 genome, leading to the emergence of new variants, an expanded T-cell breadth plays a pivotal role in providing protection against viruses that genetically deviate from the original strains [22].

It is important to acknowledge that our findings are constrained by the small sample size and the short-term follow-up period. Therefore, it is imperative to evaluate the impact of vaccination on the HIV reservoir in a larger cohort with a long-term follow-up. Nonetheless, our study provides valuable insights that contribute to the existing knowledge on this subject.

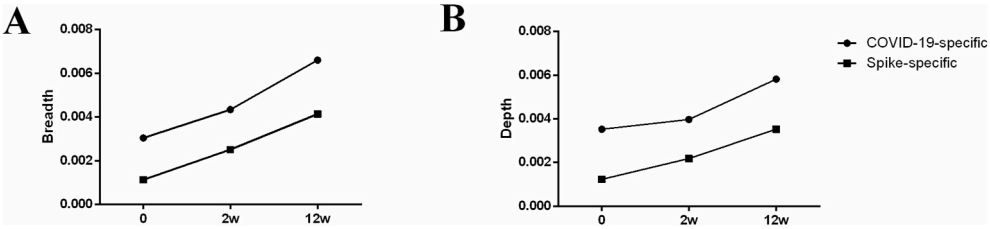

Fig. 6. Increased Clonal Breadth and Depth of COVID-19-specific TCR.
The breadth (A) and depth (B) of COVID-19-specific TCRs were measured and plotted. In the figure, circles represent TCRs specific to epitopes based on the open reading frame of the COVID-19 genome, while squares represent TCRs specific to epitopes based on the spike protein of COVID-19.

5. Conclusions

In conclusion, our study revealed an initial rise in CA HIV RNA, HIV DNA, and TCR repertoire diversity after CoronaVac vaccination in PLWHs. Furthermore, we observed an expansion in both the depth and breadth of COVID-19-specific T-cell clones in vaccinated PLWHs. These findings contribute to a more comprehensive understanding of the role of T cell immunity in COVID-19 vaccination among PLWHs.

Ethics declarations

This study was reviewed and approved by the institutional review boards of the First Affiliated Hospital, School of Medicine, Zhejiang University with the approval number: [2021376].

All participants provided written informed consent to participate in the study.

All participants provided written informed consent for the publication of their anonymous case details and images.

Data availability

The datasets used in this study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Xiaorong Peng: Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Xueling Zhu:** Writing – review & editing, Investigation, Data curation. **Xiang Liu:** Writing – review & editing, Resources, Investigation, Data curation. **Ying Huang:** Writing – review & editing, Resources, Investigation. **Biao Zhu:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30394.

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