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Clinical and immunological insights into SARS-CoV-2 reinfection: a propensity score-matched cohort study

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Abstract

Background The global circulation of SARS-CoV-2 has led to an increasing number of reinfections, raising concerns about their clinical and immune consequences. Understanding the differences in disease severity, vaccination impact, and immune response between primary infections and reinfections is essential for guiding public health strategies.

Methods We conducted a retrospective cohort study of hospitalized COVID-19 patients at Beijing Ditan Hospital from January 2023 to June 2024. SARS-CoV-2 reinfection cases were matched 1:2 with primary infection cases using nearest neighbor propensity score matching (PSM) to balance age, sex, and comorbidities between the groups. Clinical characteristics, laboratory findings, serum antibody levels, lymphocyte subsets, and the impact of vaccination on disease severity were analyzed.

Results A total of 907 patients were included, comprising 821 with primary infection and 86 with reinfection. After matching, 131 cases remained in the primary infection group and 75 in the reinfection group. No significant differences were observed in disease severity, mortality, or most clinical symptoms. Trend analysis revealed that an increasing number of vaccine doses was significantly associated with a decreasing trend in severe disease in both the primary infection group ($P=0.0221$) and the reinfection group ($P=0.0449$). IgG levels were significantly higher in reinfected patients ($P<0.001$), whereas IgM levels showed no significant difference ($P=0.474$). Among patients with primary infection, severe cases exhibited lower T cell counts than non-severe cases ($P<0.001$), but no significant differences in T cell subsets were observed between non-severe and severe reinfections.

Conclusions The higher IgG levels in reinfected individuals suggest a robust immune memory response, while T cell depletion plays a crucial role in severe primary infections. Vaccination provided a protective effect against severe disease in both primary and reinfected individuals, with a significant decreasing trend in severe/critical cases as the number of vaccine doses increased.

Keywords COVID-19, Reinfection, Propensity score matching

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Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), continues to challenge global health systems on an unprecedented level. Despite widespread vaccination campaigns and the development of effective therapeutics, the emergence of multiple infections with SARS-CoV-2 has become a significant public health concern [1].

A significant proportion of the Chinese population has experienced at least one SARS-CoV-2 infection, with a substantial number of cases occurring after the widespread outbreak of the Omicron variant in December 2022 [2]. A longitudinal study following a cohort of healthy individuals for over 35 years revealed that reinfections occur with all four seasonal human coronaviruses, most frequently at 12 months after the initial infection, suggesting that reinfection is a common characteristic of human coronaviruses, including SARS-CoV-2 [3]. Building upon this, the first documented case of SARS-CoV-2 reinfection was reported in Hong Kong in August 2020. It involved a 33-year-old male who remained asymptomatic during the second infection, with genomic sequencing confirming that the two infection episodes were caused by distinct SARS-CoV-2 strains [4]. Since this initial report, many countries have documented cases of reinfection, further underscoring the potential for recurrent SARS-CoV-2 infections worldwide [5, 6].

Current studies suggest that rates of hospitalization and mortality are substantially lower in individuals who experience reinfection compared to those with primary infection [7]. Additionally, COVID-19 reinfection has better clinical outcomes compared to primary infection in solid organ transplant recipients [8]. However, some published studies indicate that the severity of reinfection is comparable to that of the primary infection [9]. Previous studies demonstrated that Omicron variants present a significantly higher risk of reinfection compared to other SARS-CoV-2 variants [10]. Given this increased risk, several systematic reviews have assessed the effectiveness of vaccines in preventing infection and disease caused by the Omicron variant [11]. Findings indicate that reinfections were significantly more frequent among unvaccinated individuals and were associated with a higher risk of hospitalization compared to those who were vaccinated [12]. Furthermore, evidence indicates that reinfection can occur despite the presence of SARS-CoV-2 specific antibodies in their sera [13]. Additionally, the protection conferred by both vaccination and prior infection against reinfection was limited [14]. Current evidence suggests that SARS-CoV-2 reinfection is influenced by several factors, including being unvaccinated the presence of infection-induced immunity, female sex, the emergence of immune-evasive variants such as Omicron, and being over 60 years of age [15, 16]. Among individuals aged 60–74 years and those with immunocompromised conditions, the risk of mortality was significantly higher in the reinfection group than in the primary infection group [17]. Individuals with hybrid immunity, acquired through infection followed by vaccination, exhibited the strongest spike protein-specific antibody response and a distinct profile of CD4 + T cells and B memory cells [18]. Another study emphasized that reinfection is associated with a higher risk of death, hospitalization and lasting complications, regardless of infection severity, with cumulative risks and health burdens steadily increasing with each additional episode [19].

Given the continued global spread of the Omicron variant and the increasing prevalence of reinfections, it is crucial to compare the clinical characteristics of primary infection and reinfection, analyze the impact of vaccination on severe/critical cases, and assess the role of different antibody levels (IgG/IgM), immune cells, and clinical laboratory results in multiple infections. These insights are essential for developing effective strategies to curb the spread of SARS-CoV-2 and mitigate its public health impact.

Methods

Study design and participants

This retrospective observational clinical cohort study included COVID-19 patients hospitalized at Beijing Ditan Hospital between January 2023 and June 2024. The initial SARS-CoV-2 infections in patients who experienced reinfection occurred following the relaxation of China's epidemic control measures in December 2022. The inclusion criteria consisted of patients with laboratory-confirmed SARS-CoV-2 infection, as determined by reverse transcription polymerase chain reaction (RT-PCR) testing during hospitalization, with cycle threshold (Ct) values below 35 for both the ORF1ab and N genes.

The exclusion criteria were defined as follows: (1) patients under 18 years of age, (2) concurrent infections with other viruses, (3) patients undergoing active treatment for malignant tumors, (4) acquired immunodeficiency syndrome, and (5) those with severe hepatic or renal dysfunction.

Data collection

Clinical data were collected from medical records and included demographic characteristics, epidemiological history, comorbidities, vaccination status, laboratory test results, treatments, chest CT findings, and clinical outcomes. Patient data were followed until hospital discharge or death. Baseline laboratory results were defined as blood tests performed within the first 48 h after hospital admission, including routine hematological and biochemical parameters, antibody levels, and lymphocyte

subsets. All recorded vaccinations involved inactivated SARS-CoV-2 vaccines (CoronaVac by Sinovac or BBIBP-CorV/WIBP-CorV by Sinopharm).

Definition

According to the 10th version of Chinese interim guidelines for diagnosis and treatment for COVID-19, Severe COVID-19 was defined by the presence of at least one of the following clinical criteria: (1) respiratory rate > 30 breaths/minute, (2) oxygen saturation ≤ 93% on room air, (3) arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ≤ 300 mmHg at rest, or (4) rapid progression of lung lesions on chest CT ≥ 50% within 24–48 h. Critical COVID-19 patients were characterized by the presence of at least one of the following clinical manifestations: (1) respiratory failure necessitating mechanical ventilation, (2) shock, or (3) multiorgan failure or severe dysfunction.

SARS-CoV-2 reinfection is defined as any positive RT-PCR test (Ct values < 35) more than 90 days from first episode, regardless of symptoms [20].

Ethics approval and consent to participate

This study was approved by the institutional review board of Beijing Ditan Hospital, Capital Medical University and conducted in accordance with the Declaration of Helsinki (NO.DTEC-KY2024-035-01). All patients provided informed consent at admission for the storage and research use of their clinical data.

Propensity score matching

PSM was applied to eliminate the influence of baseline characteristics, ensuring comparability between the groups [21]. Propensity scores were calculated using a logistic regression model that incorporated sex, age, and comorbidities as covariates. These covariates are shown in Table 1. A 1:2 nearest neighbor matching method with a caliper of 0.2 times the standard deviation (SD) of the logit was applied, and matching was performed without replacement [22]. The PSM analysis was conducted using the MatchIt and Matching package in R software.

Statistical analysis

Categorical variables are described using frequencies and percentages, and group differences were analyzed using the Chi-square test or Fisher's exact test. Continuous variables were expressed as means ± standard deviations or as medians with interquartile ranges(IQR), and differences between groups were assessed using either Student's t test or Mann-Whitney U test. All tests were two-sided, and P values <0.05 were considered statistically significant. Statistical analysis was conducted using SPSS (version 29.0.1, IBM), and data visualization was performed with R software(version 4.4.2).

Results

Baseline characteristics

From January 2023 to June 2024, a total of 1063 patients were admitted to our hospital with SARS-CoV-2 infection. After applying the inclusion and exclusion criteria, 907 patients were included in the final analysis, comprising 821 primary infections and 86 reinfections. Prior to PSM, the reinfection group had a significantly higher age compared to the primary infection group (P<0.001). Sex distribution was similar between the two groups, with males comprising 54.7% of the reinfection group and 54.8% of the primary infection group (P=0.968). There were significant differences in comorbidities, including hypertension(P<0.001), diabetes mellitus(P=0.007),

Table 1 Comparison of baseline characteristics before and after PSM analysis

Characteristics	Unmatched			Propensity score matched		
	Primary infection (n = 821)	Reinfection (n = 86)	P value	Primary infection (n = 131)	Reinfection (n = 75)	P value
Age, (years)	46.0(32.0,62.0)	72.0(51.8,84.8)	< 0.001	63.0(46.0, 82.0)	70.0(49.5,82.5)	0.433
Male, n(%)	450(54.8)	47(54.7)	0.968	71(54.2)	42(56.0)	0.917
Comorbidities, n(%)						
Hypertension	179(21.8)	39(45.3)	< 0.001	48(36.6)	33(44.0)	0.372
Diabetes mellitus	104(12.7)	20(23.2)	0.007	8(6.1)	8(10.7)	0.365
Hyperlipidemia	37(4.5)	12(14.0)	< 0.001	22(16.8)	17(22.7)	0.395
Coronary artery disease	46(5.6)	14(16.3)	< 0.001	20(15.3)	11(14.7)	1.000
Severe/Critical, n(%)	142(17.3)	14(16.3)	0.450	36(27.5)	12(16.0)	0.088
Death, n(%)	17(2.1)	4(4.7)	0.130	9(6.9)	4(5.3)	0.773
From onset to admission, (d)	3.0(1.0,7.0)	3.0(2.0,7.0)	0.115	4.0(2.0,8.0)	3.0(2.0,6.8)	0.877
Hospitalization duration, (d)	25.0(15.0,37.0)	8.0(6.0,12.8)	< 0.001	19.0(11.0,35.0)	8.0(6.0,12.0)	< 0.001
Peak temperature, °C, Mean ± SD	38.2(37.8,38.7)	38.6(38.0,39.0)	< 0.001	38.5(38.0,38.9)	38.6(38.0,39.0)	0.080
BMI	24.7 ± 4.4	23.0 ± 3.5	0.002	24.8 ± 5.0	23.1 ± 3.6	0.031

BMI body mass index *SD* standard deviation

hyperlipidemia(P<0.001), and coronary heart disease(P<0.001), between the two groups.

After matching, 131 cases remained in the primary infection group and 75 in the reinfection group. Table 1 presents the baseline characteristics before and after matching. There were no significant differences between the two groups in terms of age, sex distribution, hypertension, diabetes mellitus, hyperlipidemia, or coronary heart disease(P>0.05). To further assess the quality of matching, we calculated the standardized mean differences (SMDs) for all covariates before and after matching, all covariates achieved an absolute SMD< 0.1 after matching (Supplementary Table 1). A Love plot was also generated to visually depict the improvement in balance (Supplementary Figure 1). Additionally, the incidence of severe/critical cases, mortality, time from symptom onset to admission, and peak temperature did not significantly between primary infections and reinfections(P>0.05). However, the reinfection group had a significantly shorter hospitalization duration compared to the primary infection group(P<0.001). Moreover, individuals in the reinfection group had a higher body mass index(BMI) than those in the primary infection group(P=0.031) (Table 1).

Clinical manifestations in the primary infection and reinfection groups

Among the 206 patients analyzed, the most frequently reported clinical symptoms were fever (73.3% vs. 85.3%) followed by cough(64.1% vs. 72.0%), expectoration(45.0% vs. 57.3%) and weakness(32.1% vs. 38.7%) in the primary infection and reinfection groups, with no statistically significant differences in their incidence rates (P > 0.05) (Fig. 1)

Comparison of laboratory parameters between two groups

Baseline laboratory findings were compared between the primary infection and reinfection groups. The reinfection group exhibited significantly lower levels of lactate dehydrogenase (LDH), creatine kinase (CK), and CK-MB compared to the primary infection group(P < 0.05). Additionally, hemoglobin (HGB) and albumin (ALB) levels were significantly decreased in the reinfection group(P < 0.05). However, no significant differences were observed between the two groups in white blood cell (WBC), neutrophil count, lymphocyte count, platelet (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), serum amyloid A (SAA), creatinine (CREA), glucose, D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin (TBIL) (P > 0.05) (Fig. 2)

The association between vaccine doses and severe/critical case proportion

The trend analysis was conducted to compare the number of vaccine doses received and the proportion of severe/critical cases between the primary infection and

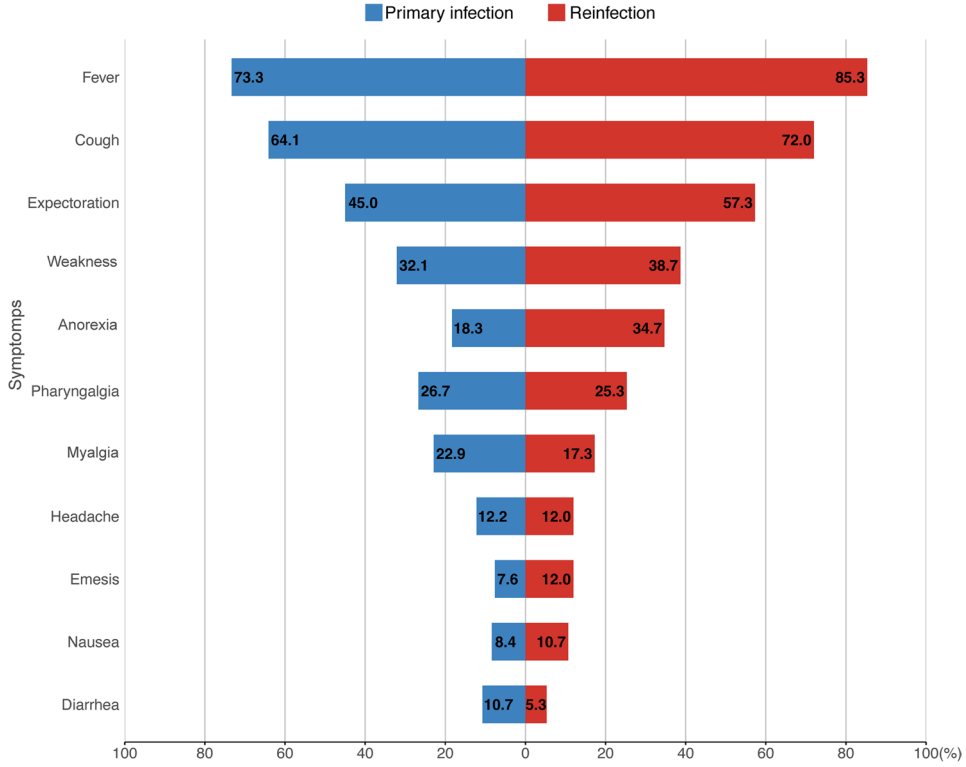

Fig. 1 Back-to-back bar chart demonstrating symptom distribution between the primary and reinfection groups

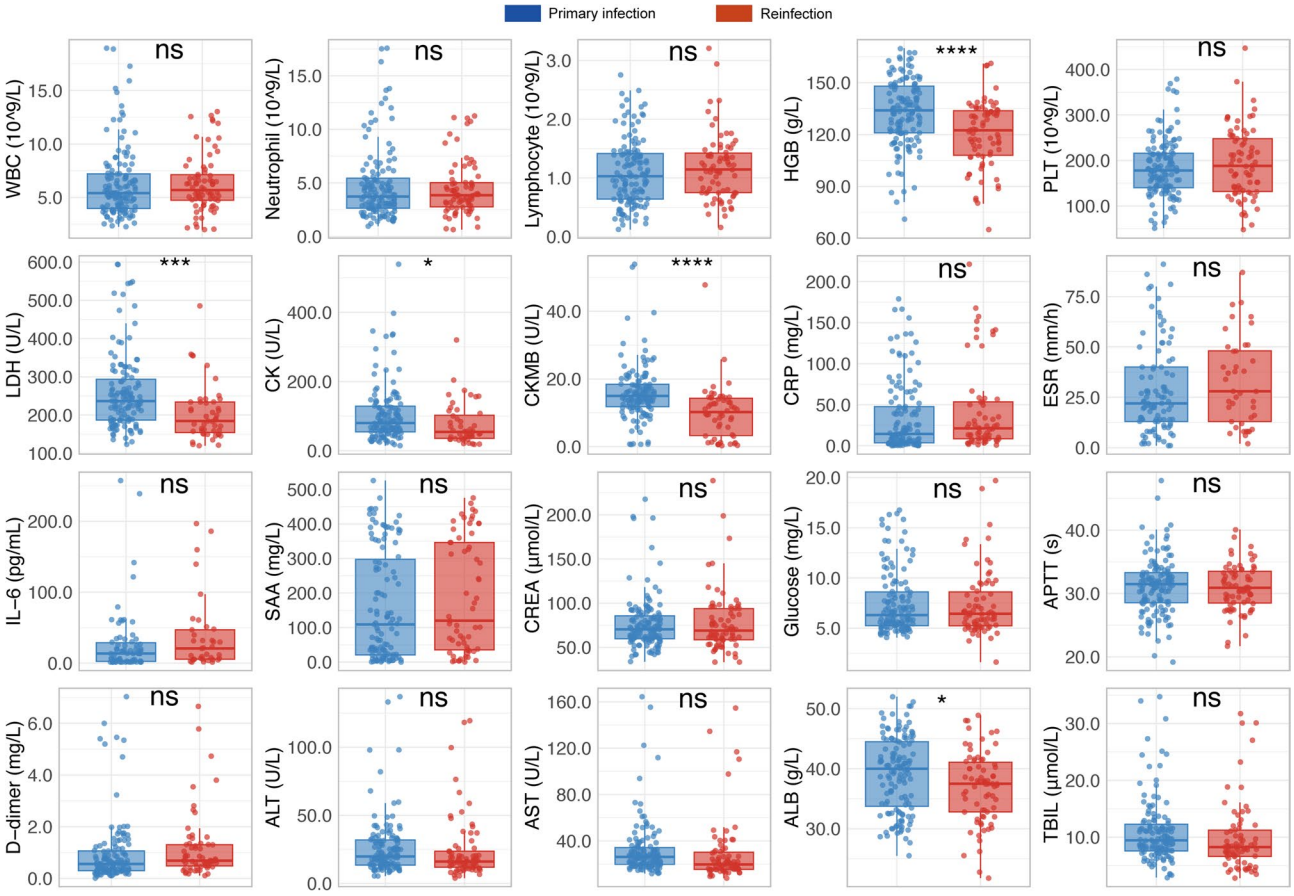

Fig. 2 Comparison of laboratory test results between primary infection and reinfection groups. WBC, white blood cell; HGB, hemoglobin; PLT, platelet; LDH, lactate dehydrogenase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; SAA, serum amyloid A; CREA, creatinine; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin. *$P<0.05$, **$P<0.01$, ***$P<0.001$. NS, not significant

reinfection groups, respectively. In the primary infection group, an increasing number of vaccine doses was significantly associated with a lower risk of severe/critical illness ($P=0.0221$), with an odds ratio of 0.572 (95% CI: 0.343–0.916). Similarly, in the reinfection group, increasing vaccine doses exposure was also associated with reduced severity ($P=0.0449$), with an odds ratio of 0.492 (95% CI: 0.226–0.985) (Fig. 3)

Comparison of serum antibody levels between primary and reinfected COVID-19 patients

We conducted a comparative analysis of serum SARS-CoV-2 IgG and IgM antibody levels between the primary infection and reinfection groups. The results indicated that IgM levels did not differ significantly between the two groups ($P=0.474$). Conversely, IgG levels were significantly higher in the reinfection group compared to the primary infection group ($P<0.001$)(Fig. 4)

Comparison of the key characteristics of peripheral blood lymphocyte subsets

Patients were categorized into four subgroups based on disease severity (severe/critical vs. non-severe/critical) and infection status(primary infection vs. reinfection). In the primary infection group, severe/critical patients had significantly lower absolute counts of lymphocytes ($P<0.001$) compared to non-severe/critical patients, including total T cells ($P<0.001$), $CD4^+$ T cells ($P<0.001$), $CD8^+$ T cells ($P<0.001$), and B cells ($P<0.01$). However, no significant differences in natural killer (NK) cell counts were observed between non-severe/critical and severe/critical cases($P>0.05$). In the reinfection group, no significant differences were observed in T cell subsets (including $CD4^+$ and $CD8^+$ T cells), B cells, or NK cells between non-severe/critical and severe/critical cases($P>0.05$). Moreover, no significant differences in lymphocyte subset counts were observed between severe/critical cases of primary infection and reinfection groups($P>0.05$) (Fig. 5)

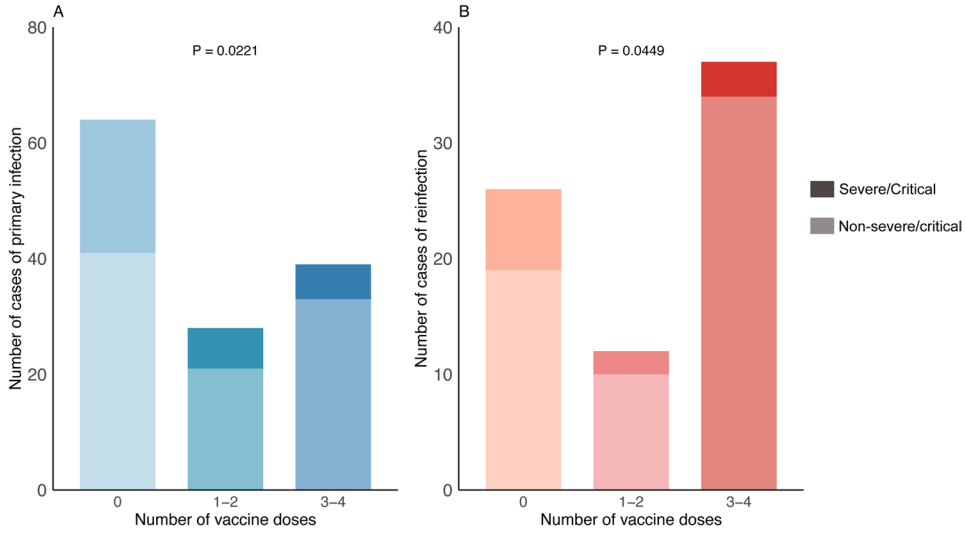

Fig. 3 Proportional bar charts of severe/critical case proportions by vaccine doses in primary infection (**A**) and reinfection (**B**) groups.

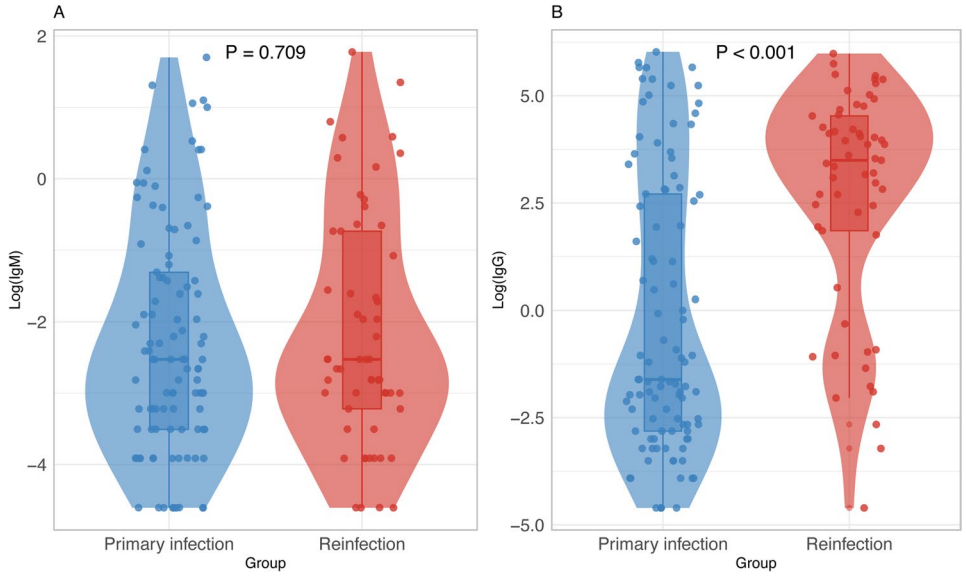

Fig. 4 Violin plots illustrating differences in antibody levels between primary infection and reinfection groups. **A** Comparison of IgM levels between the two groups. **B** Comparison of IgG levels between the two groups. Following logarithmic conversion of results

Discussion

The ongoing global circulation of SARS-CoV-2 remains a significant public health concern. Understanding whether individuals with prior infection are susceptible to reinfection, the incidence and severity of reinfection, and the prognostic implications of natural and hybrid immunity in reinfected patients has become increasingly critical. Evidence indicates that the Omicron variant of SARS-CoV-2 has an elevated risk of reinfection [23]. Further in-depth research is necessary to elucidate the long-term impact of SARS-CoV-2 reinfection and to inform future public health strategies.

In this retrospective study of 907 COVID-19 patients, including 821 with primary infection and 86 with reinfection. We observed that reinfected patients were older than those with a primary infection, age could be a confounding factor. Moreover, reinfected patients had higher rates of comorbidities such as hypertension, diabetes, hyperlipidemia, and coronary heart disease compared to primary infection patients. An Indian study also reported that hypertension was the most common comorbidity among recovered COVID-19 patients, followed by diabetes, dyslipidemia, and coronary artery disease [24]. Previous study has identified older age, sex, and underlying comorbidities as key risk factors for disease severity upon reinfection [25]. To account for these confounders, we applied PSM to enhance the comparability between groups and to enable a more accurate

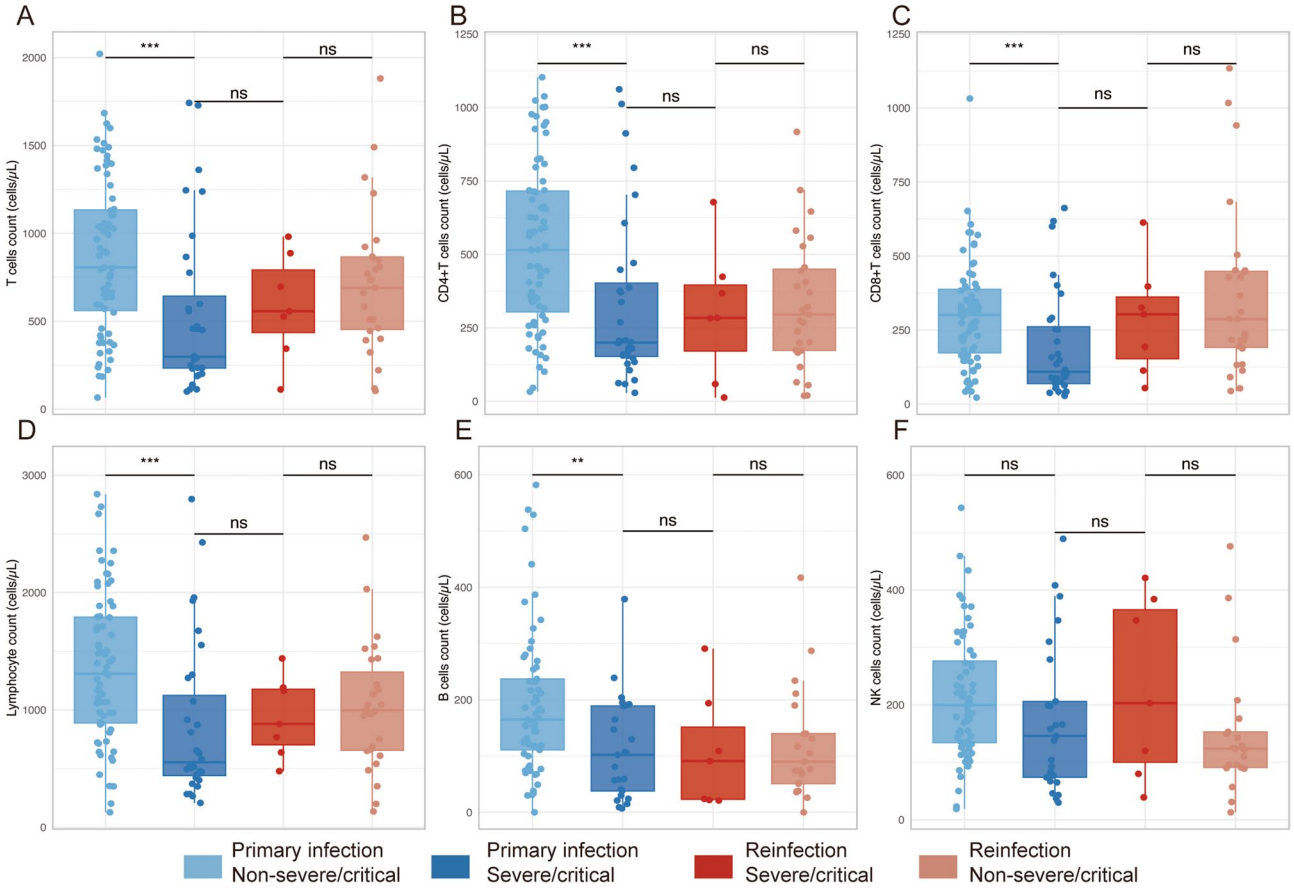

Fig. 5 Absolute count of peripheral blood lymphocyte subsets between four categories of infection: Primary infection, non-severe/critical; Primary infection, severe/critical; Re-infection, severe/critical; Re-infection, non-severe/critical. **A** Comparison of T cell absolute counts (**B**) Comparison of CD4+ T cell absolute counts. **C** Comparison of CD8+ T cell absolute counts. **D** Comparison of lymphocyte cell absolute counts. **E** Comparison of B cell absolute counts. **F** Comparison of NK cell absolute counts. Significance of data differences was determined by the Mann–Whitney test.*P<0.05, **P<0.01, ***P<0.001. NS, not significant

evaluation of other contributory factors. After PSM, 131 primary infection patients and 86 reinfection patients were included in the analysis, eliminating potential biases from baseline characteristics. Then we performed a comprehensive evaluation of clinical characteristics, laboratory findings, immune responses, and vaccination effects in primary and reinfected COVID-19 patients.

In this study, all cases were infected with the Omicron variant. We found no significant differences in disease severity between the primary infections and reinfections, which was align with previous studies suggesting that the severity of COVID-19 reinfection is comparable to that of primary infection [26]– [27]. However, other studies indicate that reinfections tend to be milder [28]. A study from Qatar reported a median interval of 277 days between primary infection and reinfection, with the odds of severe disease during reinfection being 0.12 times lower than those observed during the primary infection (95%CI, 0.03–0.31). Moreover, reinfections were associated with a 90% reduction in the odds of hospitalization or death compared to primary infections [7]. The protection conferred by previous infection against hospitalization or death due to reinfection remained robust, regardless of the SARS-CoV-2 variant [29]. Reinfection did not contribute to an increased risk of hospitalization, ICU, or death [30].

The hospitalization duration for reinfected patients was significantly shorter than that for those with primary infection, which may be related to China's pandemic control policies at the time. During the early phase of the outbreak, stringent measures were enforced, requiring patients to remain hospitalized until they tested negative for SARS-CoV-2 nucleic acid on two consecutive occasions [31], potentially prolonging hospital stays for primary infection cases. As pandemic control policies evolved and discharge criteria were gradually relaxed, reinfected patients likely experienced shorter hospitalization periods. In our study, reinfected patients had a significantly lower BMI compared to those with primary infection. A large population-based cohort study revealed that individuals with underweight or obesity faced a higher risk of hospitalization or death from COVID-19

compared to those with a healthy weight [32]. Lin et al. conducted a follow-up study and reported that 80.7% of reinfected patients experienced either milder or similar clinical symptoms compared to their primary infection [33].

Regarding laboratory findings, reinfected patients exhibited lower levels of HGB, LDH, CKMB, CK, and ALB compared to primary infected patients. However, all values remained within the normal reference range. Notably, there were no significant differences in CRP, ESR, and serum amyloid A (SAA) levels between primary and reinfected patients. Nevertheless, all three markers were significantly elevated beyond the normal reference range. A study by Ana et al. demonstrated that ESR and CRP levels were elevated regardless of disease severity or the presence of comorbidities in patients with COVID-19 [34]. Previous study has reported that ESR is elevated in COVID-19, and the changes are more pronounced with other laboratory parameters in severe diseases [35]. In a recently published study, Razieh et al. demonstrated that SAA protein serves as a valuable biomarker for the diagnosis of COVID-19, and its quantitative levels can help predict treatment outcomes in COVID-19 patients [36].

A multicenter study demonstrated that while COVID-19 vaccination does not significantly reduce disease severity, it remains effective in lowering hospitalization duration and mortality rates [37]. Our study shown that an increasing number of vaccine doses was associated with a decreasing trend in severe disease, as indicated by trend analysis, regardless of whether patients experienced primary infection or reinfection. This aligns with previous studies, which found that prior infection or two to three vaccine doses (regardless of prior infection history) provided strong protection against severe, critical, or fatal infections caused by the Omicron BA.1 and BA.2 subvariants [38]. Maram et al. found that vaccination significantly reduced hospitalization and mortality rates among reinfected individuals. Moreover, naturally acquired immunity from multiple SARS-CoV-2 reinfections, combined with vaccine-induced immunity, provided substantial protection against severe disease and mortality [39]. A nationwide retrospective cohort study reported that complete vaccination and booster doses, but not prior infection, provided protection against hospitalization and death. Furthermore, the vaccination program significantly reduced SARS-CoV-2-related mortality and hospitalizations at the population level [40]. Given the persistent risk of reinfection with emerging SARS-CoV-2 variants, and despite the effectiveness of vaccination in reducing severe disease, these findings manifest the need for the development of next-generation vaccines that provide broad protection against new variants, rather than relying on repeated booster doses of existing vaccines to combat viral evolution [41].

Our study demonstrated that IgG levels were significantly higher in the reinfection group compared to the primary infection group ($P<0.001$), while IgM levels were similar between the two groups ($P=0.474$). These findings provide crucial insights into the humoral immune response in primary and reinfected COVID-19 patients. This finding is consistent with previous studies demonstrating that reinfection with the Omicron variant in individuals with prior SARS-CoV-2 infection enhances IgG immune responses, the reinfection group exhibited higher antibody levels compared to the non-reinfection group [42]. Zeng et al. reported that SARS-CoV-2 IgG antibodies were detected in up to 82.9% of convalescent patients and remained at relatively high levels over [43]. The persistence and titers of SARS-CoV-2-specific IgG are influenced by the severity of COVID-19 [44]. A multicenter prospective cohort study demonstrated that antibody positivity serves as a reliable predictor of reduced infection risk, suggesting that antibody levels may be used as a protective marker [45]. A long-term follow-up study revealed that elevated anti-spike IgG antibody levels were associated with a reduced likelihood of reinfection [46]. Our study shown that prior exposure or vaccination enhances the immune response upon reinfection. IgG antibodies play a crucial role in long-term immunity and viral neutralization. The significant elevation in IgG levels among reinfected patients may indicate a more effective adaptive immune response.

T-cell responses have emerged as a critical focus in elucidating long-term immunity against COVID-19. The T-cell memory response is a vital component of adaptive immunity, playing a key role in limiting or preventing viral reinfection by facilitating a rapid and effective immune response upon re-exposure [47]. Severe COVID-19 is characterized by significant abnormalities in circulating immune cell subsets, including a marked reduction in multiple peripheral blood subsets of both $CD4^+$ and $CD8^+$ T cells [48]. In addition, while the prevention of symptomatic COVID-19 is primarily mediated by neutralizing antibodies, protection against severe disease is likely driven by multiple immune components, including CD4 + T cells, CD8 + T cells, and memory B cells [49, 50]. Our data suggested that T-cell responses exhibited no significant differences between patients with severe primary infection and those with severe reinfection. Moreover, in primary infection cases, T cell levels were significantly higher in non-severe patients compared to those with severe disease. This is consistent with previous findings that T-cell counts negatively correlate with survival, and CD4 + and CD8 + T lymphocytes are significantly decreased in severe diseases [51, 52]. However, among reinfected patients, there was no significant difference in T cell levels between non-severe and severe cases. Previous studies have indicated that the strength

and temporal characteristics of SARS-CoV-2-specific CD4 + and CD8 + T cell responses affect COVID-19 severity during the acute infection phase, while delayed and attenuated virus-specific CD8 + T cell responses are hallmark features of severe COVID-19 [53]. Furthermore, the severity of the primary infection has been found to inversely impact T-cell memory maintenance, thereby influencing reinfection risk in subsequent waves of emerging variants [53]. Reinfection with Omicron subvariant has been shown to promote the differentiation of virus-specific $CD8^+$ T cells [54]. Convalescent individuals from the initial SARS-CoV-2 infection retain virus-specific effector memory T cells, which can be rapidly reactivated upon re-exposure to Omicron, thereby facilitating efficient immune responses and mitigating excessive T-cell exhaustion [55].

It is important to acknowledge several limitations of this study. First, our analysis focused exclusively on hospitalized patients, excluding individuals with mild or asymptomatic infections managed in outpatient settings or through self-care. This may have resulted in an underestimation of reinfection rates and an overestimation of disease severity, particularly in populations with high levels of vaccine-induced or hybrid immunity. Accordingly, the findings may not be generalizable to the broader community-dwelling population. Second, this was a retrospective, single-centre study, which inherently limits causal inference and may introduce selection bias. Third, detailed records on the timing of vaccination and the interval between the last vaccine dose and reinfection were unavailable, limiting our ability to assess the waning of immunity over time. Future prospective, multicenter studies with larger and more diverse cohorts are warranted to better elucidate SARS-CoV-2 reinfection patterns and associated immune responses.

Conclusions

Our results indicate that the clinical manifestations of primary infection and reinfection were largely similar. Vaccination provided a protective effect against severe disease in both primary and reinfected individuals, with a significant decreasing trend in severe/critical cases as the number of vaccine doses increased. These findings highlight the critical role of vaccination, particularly for at-risk populations, in reducing disease severity. Additionally, IgG levels were significantly higher in reinfected patients, reflecting a strong memory B cell response following prior exposure to SARS-CoV-2. Moreover, T cell depletion is a key factor associated with severe primary infection but may be less relevant in reinfections, suggesting that pre-existing immune memory may help compensate for adaptive immune deficiencies, thereby reducing disease severity.

Abbreviations

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PSM	Propensity score matching
RT-PCR	Reverse transcription polymerase chain reaction
Ct	Cycle threshold
PaO_2/FiO_2	Arterial oxygen partial pressure/fractional inspired oxygen
SD	Standard deviation
BMI	Body mass index
WBC	White blood cell
HGB	Hemoglobin
PLT	Platelet
LDH	Lactate dehydrogenase
CK	Creatine kinase
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IL-6	Interleukin-6
SAA	Serum amyloid A
CREA	Creatinine
APTT	Activated partial thromboplastin time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALB	Albumin
TBIL	Total bilirubin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11398-0.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

C.Z. and Z.C. designed the study. C.Z., L.L., Z.G., J.W., R.W., Z.J., and D.T. collected the data. C.Z., L.L., and J.W. participated in statistical analysis. C.Z., L.L., and Z.G. wrote the draft of the manuscript. C.Z., D.T., and Z.C. revised the draft. Z.C. performed supervision and acquired funding. All authors contributed to the final version and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University(NO. KY2023-015) and conducted in accordance with the principles of the Helsinki Declaration.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests.

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