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ORIGINAL RESEARCH

Factors Influencing COVID-19 Viral Clearance: Implications for Vaccination and Antiviral Therapy

Jia Zeng[1,*], Heping Xu[1,*], Shuai Luo[1,*], Xiaotian Zhou[2], Xishi Li[3], Yuwen Zeng[3], Yihan Wang[2], Haotian Jiang[3], Changfeng Lin[4], Chengfang Zheng[5], Jianwen Ruan[6], Weiling Yu[7], Jinjian Yao[1], Jiannong Zhao[8]

[1]Emergency Department of Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, Hainan, 570311, People's Republic of China; [2]Emergency Trauma College, Hainan Medical University, Haikou, Hainan, 571199, People's Republic of China; [3]Emergency Department, The second Hainan Affiliated Hospital of Hainan Medical University, Haikou, Hainan, 570311, People's Republic of China; [4]Department of Infectious Diseases, Sanya Central Hospital, SanYa, Hainan, 572000, People's Republic of China; [5]Department of Infectious Diseases, Hainan Western Central Hospital, Danzhou, Hainan, 813099, People's Republic of China; [6]Department of Infectious Diseases, Haikou City People's Hospital, Haikou, Hainan, 570208, People's Republic of China; [7]Oncology Department, Haikou City People's Hospital, Haikou, Hainan, 570208, People's Republic of China; [8]Department of Neurosurgery, Hainan General Hospital, Hainan Medical University, Haikou, Hainan, 571199, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jinjian Yao, Emergency Department of Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, Hainan Province, 570311, People's Republic of China, Email 114715854@qq.com; Jiannong Zhao, Department of Neurosurgery, Hainan General Hospital, Hainan Medical University, Haikou, Hainan, 571199, People's Republic of China, Email zhaojiannong@muhn.edu.cn

Background: Understanding the factors influencing viral clearance in hospitalized COVID-19 patients, including vaccination status and antiviral therapy, is critical for optimizing clinical management.

Methods: 1,424 hospitalized COVID-19 patients retrospectively included from four tertiary hospitals in Hainan Province between March and December 2022. Viral clearance was defined as the interval from hospital admission to the first of two consecutive RT-PCR tests with Ct values ≥35. Clinical data, vaccination history, and antiviral treatment were collected. A generalized linear mixed model and Robust regression were used to assess viral clearance dynamics and their predictors.

Results: Delayed viral clearance was independently associated with advanced age ($p < 0.001$), male sex ($p = 0.006$), hypertension ($p < 0.001$), coronary heart disease ($p = 0.004$), ICU admission ($p < 0.001$), and mechanical ventilation ($p < 0.001$).Patients receiving ≥2 inactivated vaccine doses had significantly higher baseline Ct values (median 29.75 vs 28.75, $p = 0.014$), shorter time to viral negativity (6.3 vs 7.4 days, p < 0.001), and reduced hospital stay (11.2 vs 12.7 days, $p < 0.001$). Among these, patients vaccinated ≥360 days prior had shortest negative conversion time (5.6 days) and shortest hospitalization (10.3 days).Antiviral therapy with Nirmatrelvir-ritonavir (N/R) accelerated viral clearance more effectively than Azvudine (2.29 vs 1.82 Ct/day, $p = 0.045$) and no antiviral treatment (1.88 Ct/day, $p = 0.041$), Although NAT-treated patients achieved viral negativity more rapidly (6.2 days, p = 0.013), N/R demonstrated superior clearance rate. Hospital stays were shorter with N/R than Azvudine (12.1 vs 13.5 days, $p = 0.015$).

Conclusion: Viral clearance dynamics in hospitalized COVID-19 patients are influenced by age, comorbidities, vaccination, and antiviral treatment. Administration of ≥2 inactivated vaccine doses—especially ≥360 days apart—and early N/R therapy may accelerate viral clearance and reduce hospital stay.

Keywords: inactivated COVID-19 vaccine, comorbidities, viral clearance, antiviral drugs

Introduction

SARS-CoV-2 persists globally, albeit with reduced transmission intensity.[1] Despite widespread vaccination and antiviral use having alleviated the overall burden of COVID-19,[2] a detailed understanding of viral clearance dynamics remains critical. Viral load not only correlates with disease severity,[3] transmissibility, and treatment response,[4–6] but also serves as a proposed surrogate marker for therapeutic efficacy. Accordingly, elucidating the kinetics of viral decline is essential for informing clinical decision-making.

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Certain populations are disproportionately affected by severe COVID-19. Elderly individuals are more likely to develop acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), while male sex is consistently associated with worse outcomes.[7–10] Children, by contrast, exhibit more robust immune responses and milder disease courses.[8,11] Comorbidities such as hypertension, coronary heart disease (CHD), and diabetes further increase severity risks.[12] However, how these factors influence viral clearance dynamics remains poorly understood—representing a crucial gap in tailoring patient-specific therapeutic strategies for those underlying conditions.

Vaccination continues to serve as the cornerstone of COVID-19 prevention. Although mRNA vaccines demonstrate high efficacy,[13] uncertainties persist regarding the durability of protection and optimal dosing intervals for inactivated vaccines. Addressing these knowledge gaps is crucial for maintaining herd immunity, particularly in settings where inactivated vaccines are the primary immunization strategy.

Antiviral therapies provide essential adjunctive benefits, especially among high-risk individuals with elevated viral loads. Existing evidence supports their role in reducing hospitalization rates and mortality.[14,15] Nonetheless, the comparative effects of individual antiviral agents on viral clearance dynamics remain incompletely characterized—hindering the development of precision-based antiviral strategies.

Bridging these critical knowledge gaps requires comprehensive real-world data that integrate host factors, immunization timelines, and antiviral regimens. Large-scale observational studies are urgently needed to unravel these complex interactions and inform precision-guided interventions aimed at enhancing viral clearance, shortening hospitalization, and mitigating severe disease outcomes in at-risk cohorts.

Patients and Methods

Study Design and Setting

This retrospective multicenter cohort study included 1,862 patients hospitalized with confirmed COVID-19 between March and December 2022 at four tertiary hospitals in Hainan Province, China: Hainan General Hospital, Haikou People's Hospital, Hainan Western Central Hospital, and Sanya Central Hospital. Standardized admission protocols were uniformly implemented in accordance with the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 9, China).

Eligibility Criteria

Eligible patients were aged ≥14 years, had laboratory-confirmed SARS-CoV-2 infection (via RT-PCR), classic respiratory symptoms (eg, cough, fever, or dyspnea); A positive SARS-CoV-2 nucleic acid test (RT-PCR); and Radiological evidence of pulmonary involvement on chest X-ray or ground-glass opacities on CT, and had complete medical and virological records including serial Ct values. Patients were excluded if they had lacked RT-PCR data, incomplete vaccination or treatment history, or comorbidities such as malignancy, chronic kidney disease, chronic lung disease, or immunosuppressive conditions. Following exclusions, 1,424 patients were included in the final analytic cohort.

Data Collection and Variables

Clinical and demographic data were extracted from standardized electronic health records. Variables included age, sex, comorbidities (hypertension, diabetes, coronary heart disease), ICU admission, mechanical ventilation, COVID-19 vaccination status (Unvaccinated, Partially vaccinated 1 dose, Fully vaccinated 2 doses, Boosted more than 3 doses, interval to infection), and antiviral treatment regimen (Nirmatrelvir/Ritonavir, Azvudine, or no therapy). Patients were stratified accordingly for comparative analysis [Figure 1].

Outcome Definitions

The primary outcome was time to viral clearance, defined as the number of days from hospital admission to the first of two consecutive negative RT-PCR tests (Ct ≥35 for ORF1ab and N genes, ≥24 hours apart). Viral clearance rate (Ct/day) was calculated from serial Ct values. The secondary outcome was hospitalization duration.

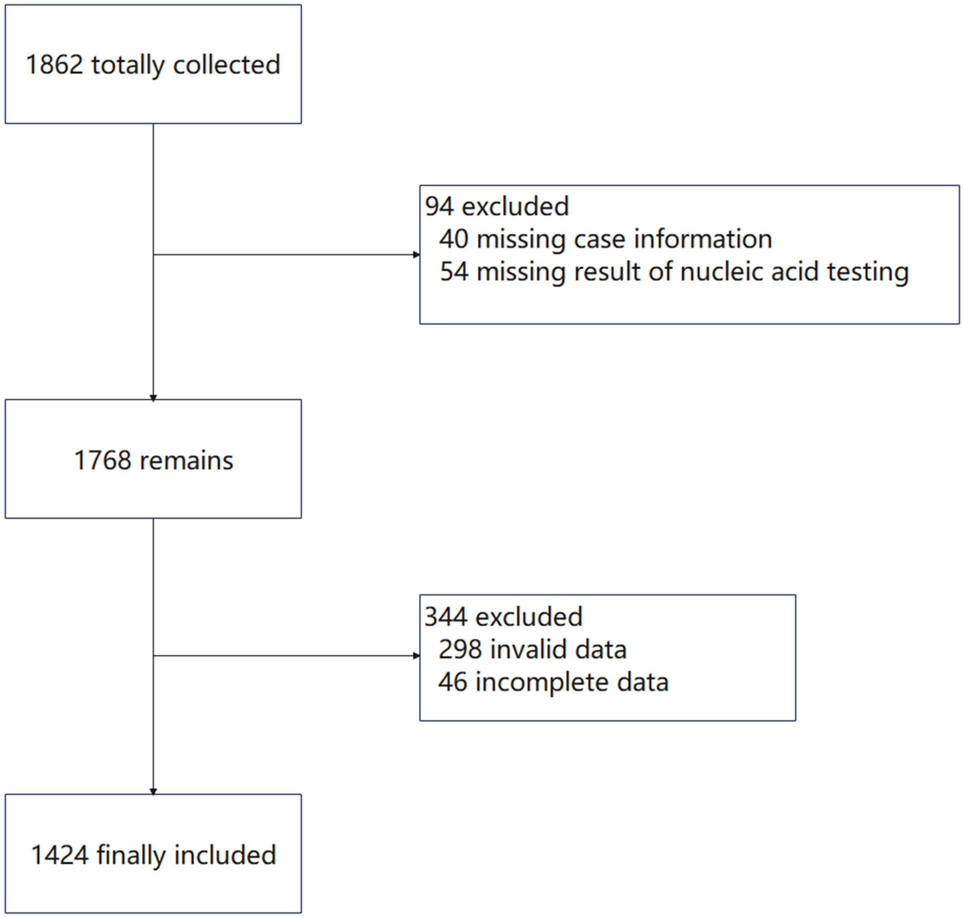

Figure 1 Workflow of study.

Viral Screen

Nasopharyngeal swabs were collected every 2–3 days. SARS-CoV-2 RNA was quantified using CFDA-approved qRT-PCR assays (GeneoDX, Shanghai; Daan Gene, Guangzhou), targeting the ORF1ab and N genes. Viral load was reported as $\log_{10}$ RNA copies/mL and Ct values. Discharge required clinical improvement, ≥3 days of normal temperature, and two negative tests ≥24 hours apart.

Ethics Approval and STROBE List

The study was approved by the Institutional Review Board of Hainan General Hospital (Approval No: Med-Eth-Re [2025]152). As this was a retrospective cohort study based on anonymized medical records, the requirement for informed consent was waived by the IRB. All patient data were de-identified prior to analysis to ensure confidentiality. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and relevant local regulations governing medical research. This study is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement for cohort studies in Supplementary Table 1.

Statistical Analysis

All Statistical analyses were conducted using R software (version 4.2.3), employing the tidyverse, lme4, robustbase, and ggplot2 packages. Continuous variables were summarized as means ± standard deviations or medians with interquartile ranges, depending on distribution assessed via the Shapiro–Wilk test. Categorical variables were reported as counts and percentages.

Group comparisons were performed using chi-square or Fisher's exact tests for categorical variables, and either independent-sample t-tests or Mann–Whitney *U*-tests for continuous variables, based on normality.

To examine temporal changes in viral load, a generalized linear mixed model (GLMM) was used to assess Ct value trajectories over time.

For predictors of viral clearance rate, univariate analyses were first conducted, followed by multivariate mixed-effects regression models adjusting for key confounders: age, sex, comorbidities, vaccination status, and antiviral therapy.

Additionally, robust linear regression was applied to assess the association of clinical variables with hospitalization duration and time to viral negativity, accounting for potential outliers and heteroscedasticity.

All statistical tests were two-tailed, with statistical significance defined as $p < 0.05$. Missing data were handled via complete case analysis, as the proportion of missingness was <5%.

Results

Detailed patient characteristics of 1,424 hospitalized COVID-19 patients included are provided in Table 1.

Male and Age

The male (n = 601, 42.2%) had significant slower viral clearance than female patients (*P*=0.006) as showed in trend linear [Figure 2A] and violin plots [Figure 2B], with males demonstrating a slower viral clearance rates compared to females. As shown in Figure 3A and B, higher age groups were associated with progressively slower viral clearance rates. The age group of 0–18 years old (n = 296, 20.8%) demonstrated significantly faster viral clearance compared to other age groups (0–18 years vs 18–35 years, *P*<0.001; 0–18 years vs 35–65 years, *P*<0.001; 0–18 years vs >65 years, *P*<0.001). Additionally, the age group of 18–35 years old (n = 297, 20.9%) showed faster viral clearance compared to the aged group of 35–65 years old (n = 508, 35.7%) (18–35 years vs 35–65 years, *P*<0.001). In contrast, the age group (>65 years) (n = 323, 22.7%) exhibited the slowest viral clearance rates in comparison (18–35 years vs >65 years, *P*<0.001; 35–65 years vs >65 years, *P*<0.001).

Table 1 Clinical Characteristics of the 1424 COVID-19 Patients in Hospital

		Non (N=1005)	Azvudine (N=332)	N/R (N=87)	Total
Gender (N,%)	Male	419 (69.72)	134 (22.3)	48 (7.99)	601 (42.21)
	Female	586 (71.20)	198 (24.06)	39 (4.74)	823 (57.79)
Age (Mean±sd)		40.4±24.0	51.8±18.1	49.3 ±19.1	43.6±23.0
Baseline Ct value (Mean±sd)		29.4±6.4	27.6±6.0	25.8 ±6.5	28.8±6.4
Min Ct value (Mean±sd)		25.8±5.0	23.7±4.6	22.8±5.2	25.1±5.0
Hypertension (N,%)	Non	876 (71.86)	277 (22.72)	66 (5.41)	1219 (85.6)
	Hypertension	129 (62.93)	55 (26.83)	21 (10.24)	205 (14.4)
CHD (N,%)	Non	972 (71)	315 (23.01)	82 (5.99)	1369 (96.14)
	CHD	33 (60)	17 (30.91)	5 (9.09)	55 (3.86)
Diabetes (N,%)	Non	950 (71.11)	305 (22.83)	81 (6.06)	1336 (93.82)
	Diabetes	55 (62.50)	27 (30.68)	6 (6.82)	88 (6.18)
Vaccination (N,%)	0–1 dose	485 (71.85)	158 (23.41)	32 (4.74)	675 (47.40)
	2–3 doses	520 (69.43)	174 (23.23)	55 (7.34)	749 (52.6)
ILVTI (N,%) (≥2 doses)	0–180 days	86 (63.24)	39 (28.68)	11 (8.09)	136 (9.55)
	180–360 days	333 (72.23)	94 (20.39)	34 (7.38)	461 (32.37)
	>360 days	101 (66.45)	41 (26.97)	10 (6.58)	152 (10.67)
ICU (N,%)	Non-ICU	1002 (70.96)	323 (22.88)	87 (6.16)	1412 (99.16)
	ICU	3 (25)	9 (75.0)	0 (0)	12 (0.84)
MV (N,%)	Non-MV	1003 (71.19)	321 (22.78)	85 (6.03)	1409 (98.95)
	MV	2 (13.33)	11 (73.33)	2 (13.33)	15 (1.05)

Abbreviations: ICU, Intensive Care Unit; CHD, Coronary Heart Disease; ILVTI, Interval Last Vaccination To Infection;MV:Mechanical Ventilation.

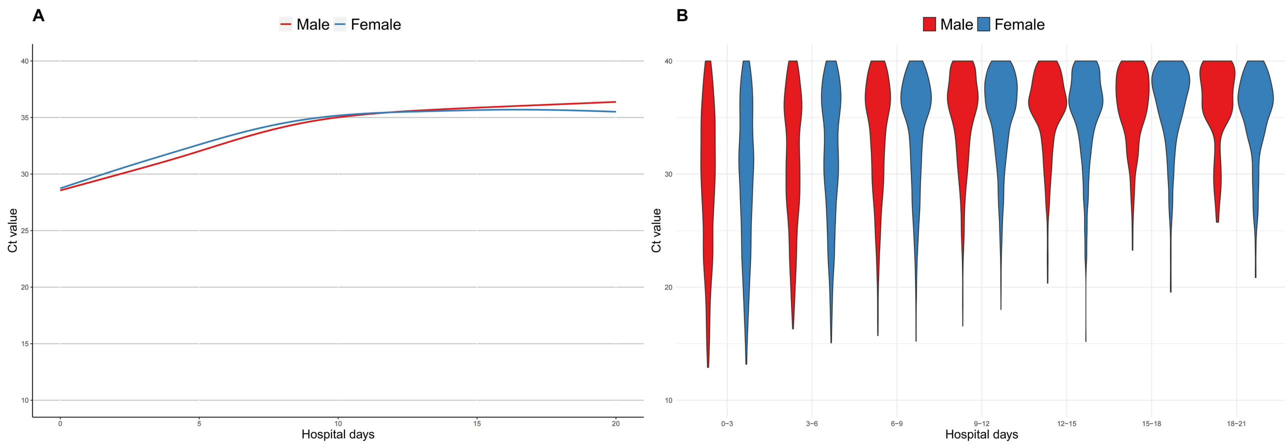

Figure 2 Effect of gender on viral clearance. (**A**) Comparison of Median Ct values over the hospitalization period between male and female. (**B**) The distribution of Ct values across hospitalization days between male and female.

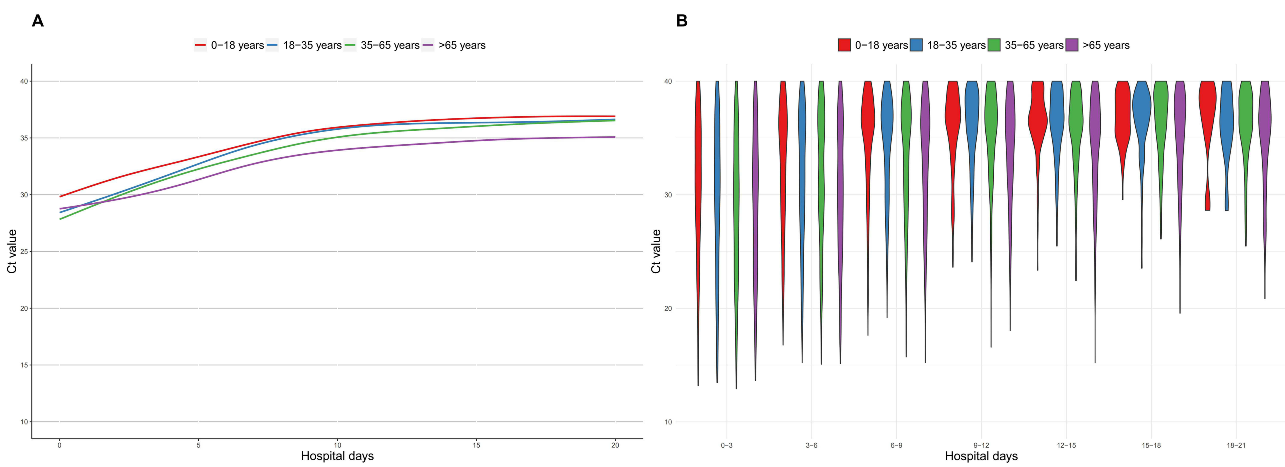

Figure 3 Effect of different age on viral clearance. (**A**) Dynamic of Median Ct values in four age groups: 0–18 years, 18–35 years, 35–65 years, and >65 years. (**B**) Ct value distributions among stratified by age groups.

Comorbidities of Hypertension, CHD and Diabetes

Patients with hypertension (n = 205,14.4%, P<0.001) [Figure 4A and B] or CHD (n = 55,3.9%, P=0.004) [Figure 4C and D] exhibited significantly reduced viral clearance rates compared to those without hypertension and CHD. Conversely, diabetes (n = 88, 6.2%) was not significantly associated with Ct dynamics (P = 0.333) in our analysis [Figure 4E and F].

Vaccination

All COVID-19 vaccines administered in China are inactivated vaccines, Figure 5 illustrates the dynamic changes in Ct values, time to viral negativity, and duration of hospitalization across vaccination groups (0–1 dose vs 2–3 doses). There was no statistically significant difference in Ct values between patients who received a single dose of the COVID-19 vaccine and those who were unvaccinated. However, patients who received 2–3 doses of the COVID-19 vaccine (n = 749,52.6%) had higher initial Ct values (Ct_{median} =29.75) compared to those vaccinated less than 2 doses (n = 675,47.4%) (Ct_{median} =28.75, P=0.014) in trend linear [Figure 5A] and violin plots [Figure 5B], but Patients with 2–3 vaccine doses showed no significant difference in viral clearance rate (P = 0.809), Moreover, vaccination 2–3 doses showed rapid in negative conversion (6.3 vs 7.4 days, P<0.001) [Figure 5C and Table 2] and decrease hospital stays (11.2 vs 12.7 days,P<0.001) [Figure 5D and Table 2] as compared to vaccination less than 2 doses.

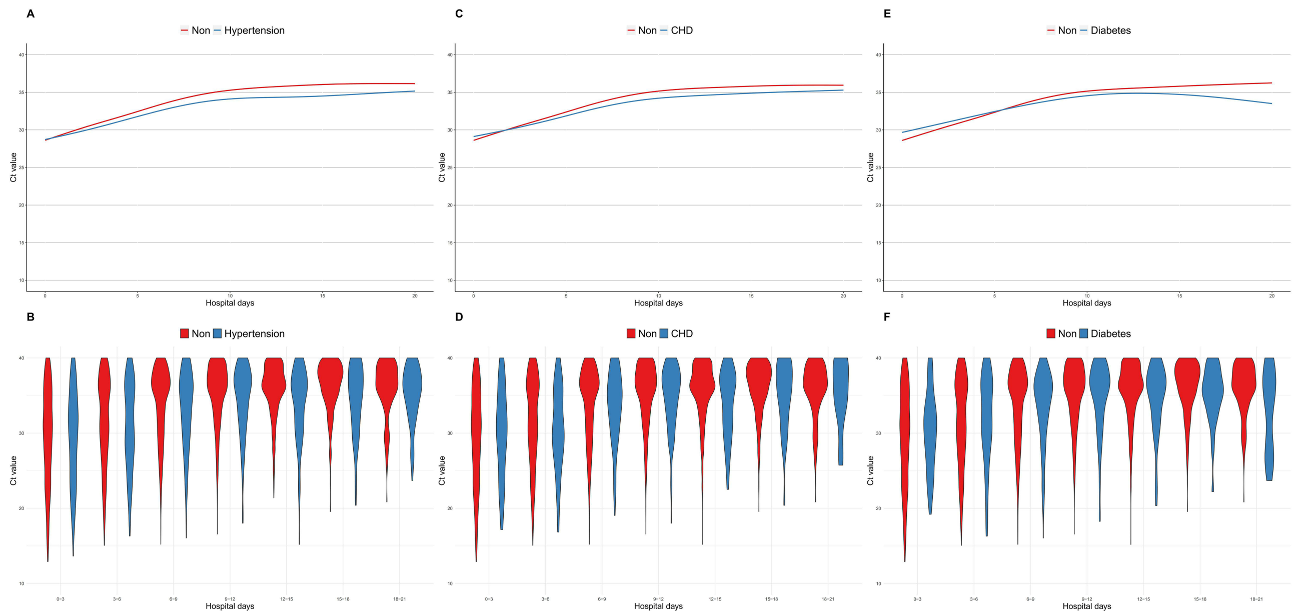

Figure 4 Effect of comorbidities on viral clearance, (**A**) Patients without hypertension exhibit significantly faster viral clearance than those with hypertension, (**B**) Ct value distributions between Non and hypertension. (**C**) Patients without CHD demonstrated significantly faster clearance than CHD, (**D**) Ct value distributions between Non and CHD. (**E** and **F**) No significant difference in viral clearance between patients with diabetes and without diabetes.

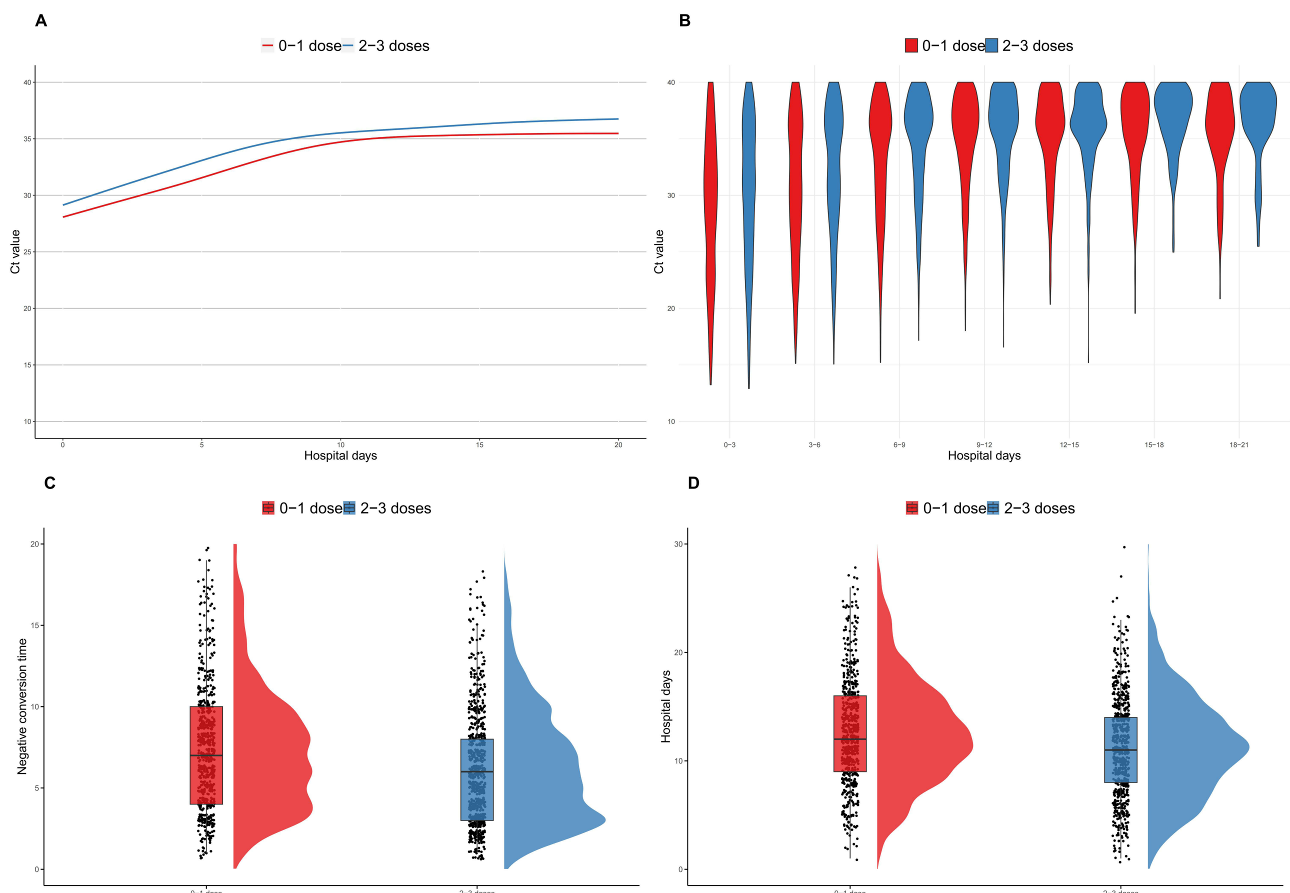

Figure 5 Effect of vaccination dose number on viral clearance. (**A**) Dynamic median Ct values over hospitalization days between 0–1 dose group and 2–3 doses group. (**B**) The distribution of Ct values between 0–1 dose group and 2–3 doses group. (**C**) Violin and box plots comparing time to viral negativity between 0–1 dose group and 2–3 doses group. (**D**) Violin and box plots comparing hospitalization duration between 0–1 dose group and 2–3 doses group.

Table 2 Effect of Vaccination Dose Number on Viral Clearance and Clinical Outcomes

	0–1 Dose (N=675)	2–3 Doses (N=749)	P
Hospital Days (Mean ±sd)	12.7 ±4.9	11.2 ±4.7	<0.001
Negative Conversion Time (Mean ±sd)	7.4 ±4.2	6.3 ±3.7	<0.001
Initial Ct value (Median [95% CI])	28.7 [28.04,29.53]	29.8 [29.31,30.17]	0.014

In patients who received 2–3 vaccine doses, the day last vaccination to hospital day divided according to 0–180 days,-180–360 days, above 360 days and 0–1dose as reference [Figure 6A and B], as shows in Table 3, those whose last vaccination occurred more than 360 days before hospitalization (n = 152 of 749, 20.3%) had highest initial Ct values (Ct_{median} =30.67) compared to those vaccinated within 360 days prior to hospitalization (0–180 days,Ct_{median} =29.59;180–360 days,Ct_{median} =29.64). This trend was consistent across comparisons, with significantly higher baseline Ct values observed in the >360 days group compared to the 180–360 days group ($P = 0.013$). Specifically, patients vaccinated over 360 days ago achieved negative conversion time in a mean of 5.6 days, significantly earlier than patients vaccinated less than 2 doses, who became viral negative in 7.4 days ($P < 0.001$) [Figure 6C]. Similarly, the mean hospital stay was shorter in patients vaccinated more than 360 days ago (10.3 days) compared to patients vaccinated less than 2 doses (12.7 days) ($P < 0.001$) [Figure 6D].

Viral Clearance

The study population included 87 patients in the N/R group (6.1%, mean [SD] age, 49.3 [19.1] years), 332 in the Azvudine group (23.3%, mean [SD] age, 51.8 [18.1] years), and 1005 in the NAT group (70.6%, mean [SD] age, 40.4 [24.0] years).

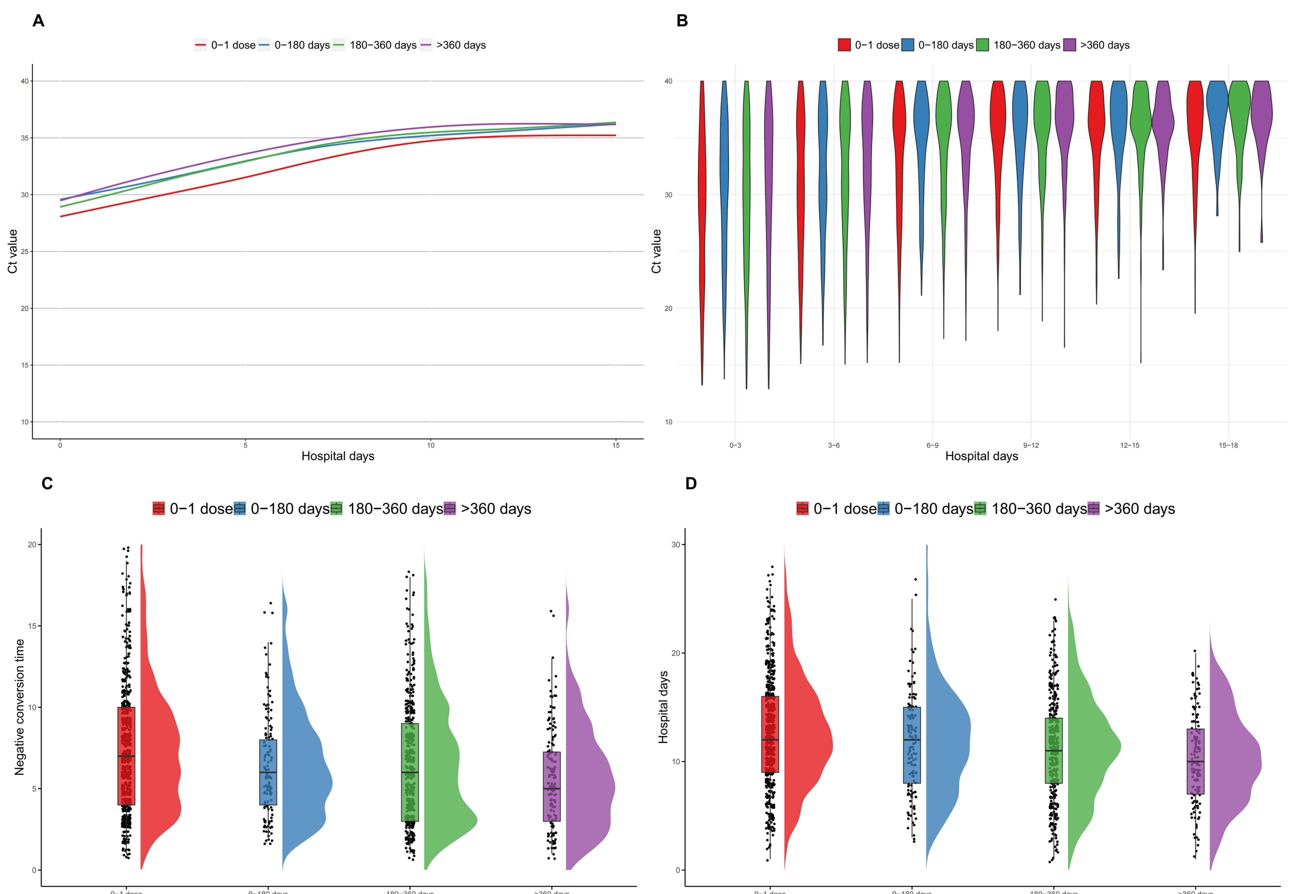

Figure 6 Effect of interval last vaccination to Infection on viral clearance. (**A**) Median Ct values stratified by vaccination intervals: 0–1 dose (reference), 0–180 days, 180–360 days, and >360 days. (**B**) Violin plot showing Ct value distributions over hospitalization days across the four age groups. (**C**) Violin and box plots comparing time to viral negativity among the four age groups. (**D**) Violin and box plots comparing hospitalization days among the four age groups.

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Table 3 Effect of Interval Last Vaccination to Infection on Viral Clearance and Clinical Outcomes

	0–1 Dose (N=675)	0–180 Days (N=136)	180–360 Days (N=461)	>360 Days (N=152)	p
Hospital Days (Mean ±sd)	12.7±4.9	11.9 ±4.8	11.2±4.9	10.3 ±4.1	<0.001
Negative Conversion Time (Mean ±sd)	7.4±4.2	6.2 ±3.4	6.0 ±3.9	5.6±3.2	<0.001
Initial Ct value (Median [95% CI])	28.7 [28.01,29.53]	29.6 [28.61,30.86]	29.6 [28.9,30.51]	30.7 [29.64,32.05]	0.089

Despite lower initial cycle threshold (Ct) values in the N/R (25.92) and Azvudine (28.62) groups compared to NAT (31.16) (N/R vs Azvudine, P = 0.007; N/R vs NAT, P<0.001) [Figure 7A], N/R demonstrated superior therapeutic effects. N/R was associated with faster viral clearance rates (2.29 vs 1.82 increase in Ct value per day for Azvudine, P = 0.045) [Figure 7B and Table 4], a shorter time to viral negativity (7.3 vs 8.5 days for Azvudine, P = 0.013) [Figure 7C and Table 4], and reduced hospital stays (12.1 vs 13.5 days for Azvudine, P = 0.015) [Figure 7D and Table 4].

Compared to NAT, the N/R group also exhibited faster viral clearance (2.29 vs 1.88 increase in Ct value per day, P = 0.041) [Table 4], but NAT patients achieved viral negativity more quickly (6.2 vs 7.3 days, P = 0.013) [Figure 7C and Table 4]. No significant difference was observed in hospital stay between the N/R and NAT groups (12.1 vs 11.4 days, P = 0.27) [Figure 7D and Table 4].

In robust regression analysis (Figure 8 and Table 5), N/R showed a significant association with shorter negative conversion time (1.09 days [95% CI: 0.29–1.88], P = 0.007), compared to Azvudine (2.10 days [95% CI: 1.56–2.64], P < 0.001).

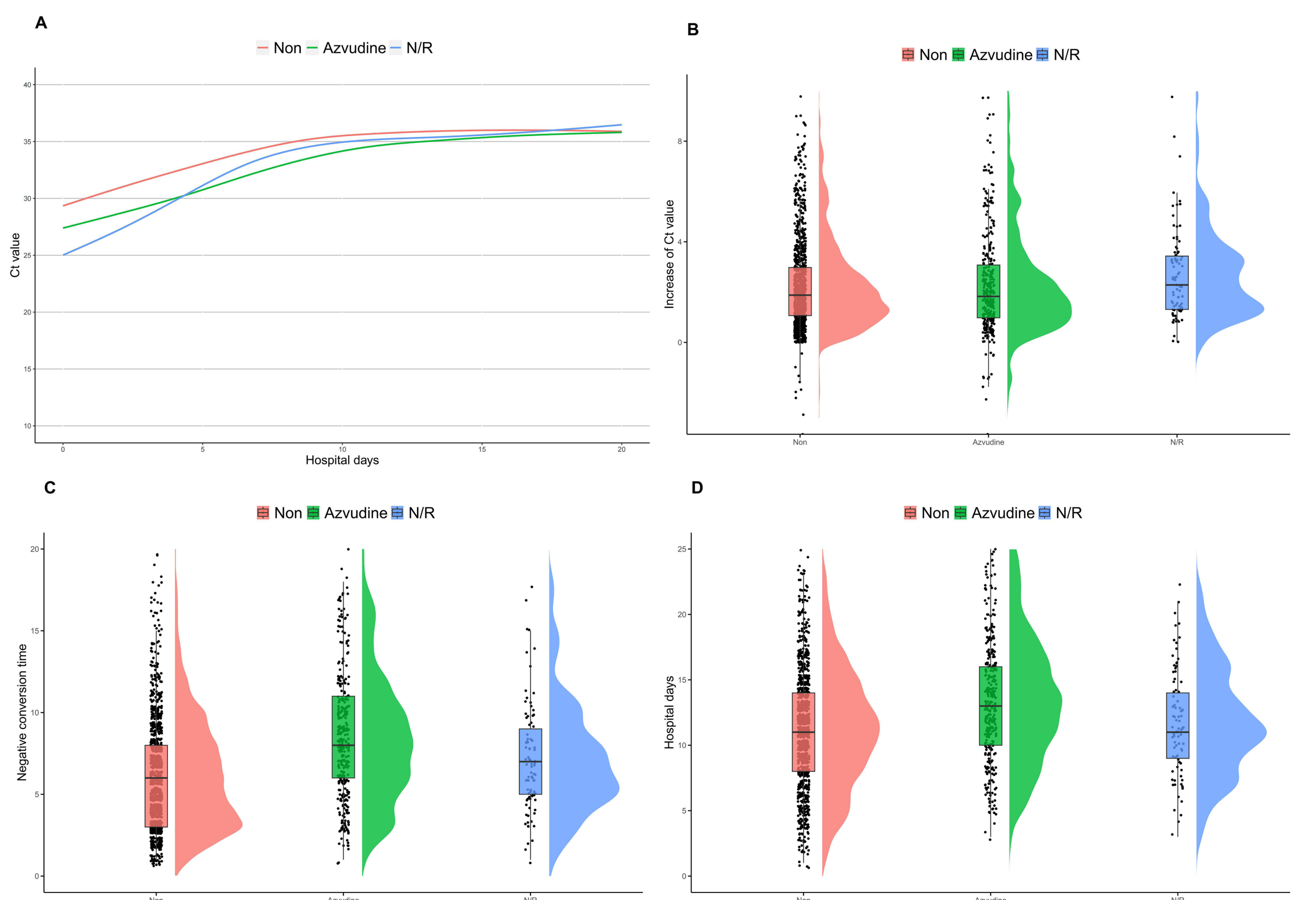

Figure 7 Effects of different antivirus regimen on viral clearance. (**A**) Dynamic median Ct values over hospitalization days for no antiviral therapy, Azvudine, and N/R groups. (**B**) Violin and box plots comparing Ct value increase rates among the three groups. (**C**) Violin and box plots comparing time to viral negativity among the three groups. (**D**) Violin and box plots comparing hospitalization days among the three groups.

Table 4 Effects of Different Antivirus Regimen on Viral Clearance

	Non (N=1005)	Azvudine (N=332)	N/R (N=87)	P
Hospital Days (Mean±sd)	11.3 ±5.0	13.5 ±4.9	12.1±4.7	<0.001
Negative Conversion Time (Mean±sd)	6.2 ±3.5	8.5±4.2	7.3±3.8	<0.001
Increase of Ct value (Median [95% CI])	1.9 [1.74,1.98]	1.8 [1.63,2.02]	2.3 [1.56 2.77]	0.027
Initial Ct value (Median [95% CI])	31.2 [30.33,31.73]	28.6 [27.26,29.87]	25.92 [24.58,28.65]	<0.001

Abbreviation: N/R, Nirmatrelvir/Ritonavir.

Vaccination with two or more doses significantly reduced time to viral clearance (–1.33 days [95% CI: –1.73 to –0.93], $P < 0.001$), with the greatest effect observed in individuals vaccinated more than 360 days prior (–1.95 days [95% CI: –2.54 to –1.36], $P < 0.001$). Age showed a positive correlation with delayed clearance (0.02 days per year [95% CI: 0.01–0.03], $P < 0.001$), while gender and comorbidities were not statistically significant.

For hospitalization stay (Figure 9 and Table 6), Azvudine was associated with prolonged hospital stays (2.12 days [95% CI: 1.49–2.75], $P < 0.001$), while N/R was not statistically significant (0.64 days [95% CI: –0.41 to 1.68], $P = 0.2309$). Receiving two or more vaccine doses significantly reduced hospital days (–1.55 [95% CI: –2.05 to –1.05], $P < 0.001$), most notably for those vaccinated over 360 days ago (–2.35 [95% CI: –3.12 to –1.58], $P < 0.001$). Age remained a minor but significant factor (0.02 per year [95% CI: 0.01–0.03], $P = 0.005$).

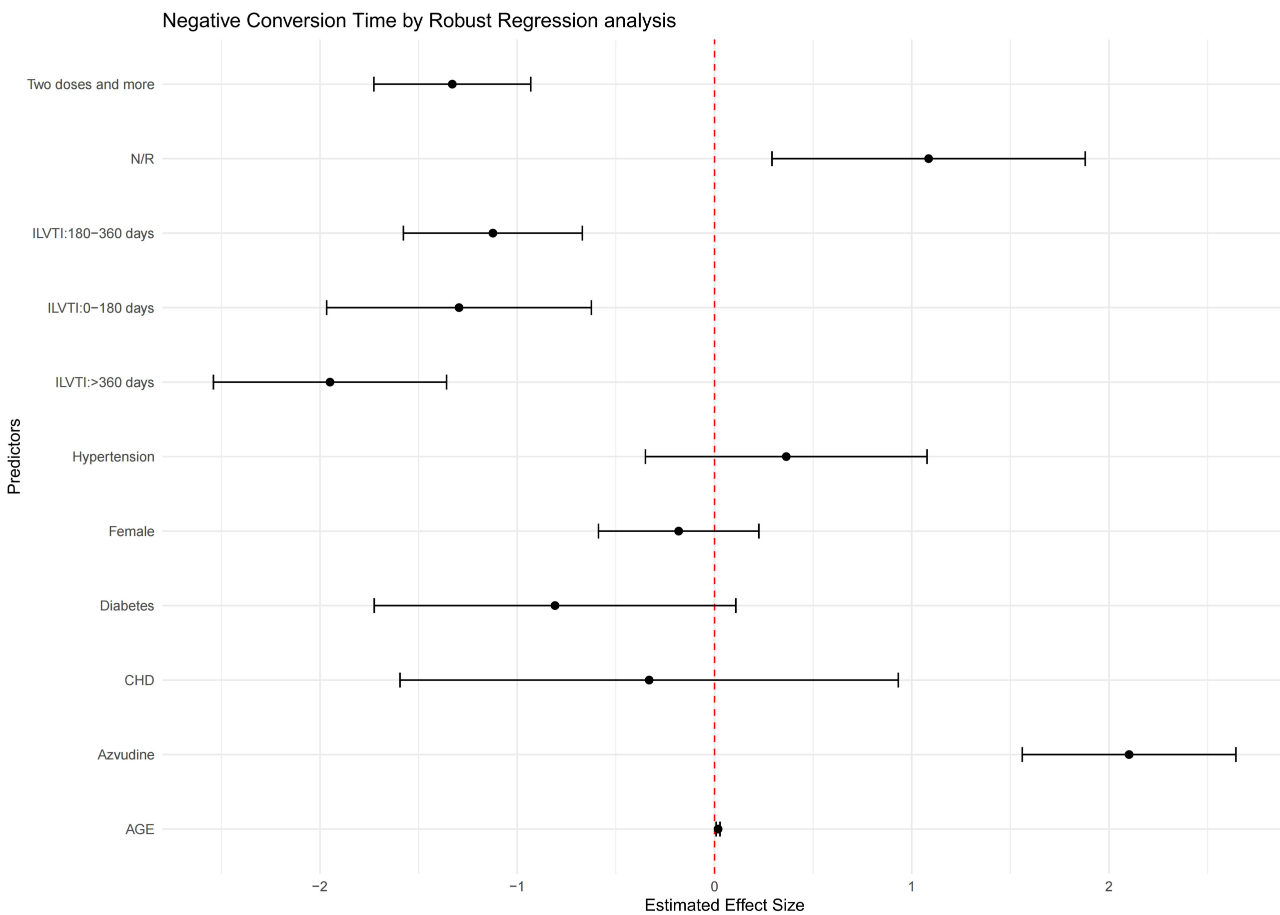

Figure 8 Influence of factors on negative conversion time based on robust regression analysis.

Table 5 Negative Conversion Time

		Robust Regression	P
Antivirus	Azvudine	2.1[1.56, 2.64]	<0.001
	N/R	1.09[0.29, 1.88]	0.007
Vaccination	2–3 doses	−1.33[−1.73, −0.93]	<0.001
ILVTI (≥2 doses)	0–180 days	−1.3[−1.97, −0.62]	<0.001
	180–360 days	−1.12[−1.58, −0.67]	<0.001
	>360 days	−1.95[−2.54, −1.36]	<0.001
Gender	Female	−0.18[−0.59, 0.22]	0.381
Age		0.02[0.01,0.03]	<0.001
Comorbidities	Hypertension	0.36[−0.35, 1.08]	0.318
	CHD	−0.33[−1.60, 0.93]	0.607
	Diabetes	−0.81[−1.73, 0.11]	0.084

Abbreviation: ILVT, Interval Last Vaccination to Infection.

ICU Admission and Mechanical Ventilation

The viral clearance rate in patients admitted to the ICU (n = 12[0.8%]) was significantly lower ($P < 0.001$) compared to non-ICU patients. ICU patients had significantly lower initial Ct values (23.3 vs 29.4), indicating higher viral load at baseline [Figure 10A]. Furthermore, patients requiring mechanical ventilation (n = 15[1.1%]) had a median Ct value of 25.7 on their first nucleic acid test, and their viral clearance rate was also significantly lower ($P < 0.001$) compared to those who did not require mechanical ventilation, with a median Ct value of 29.4 [Figure 10B].

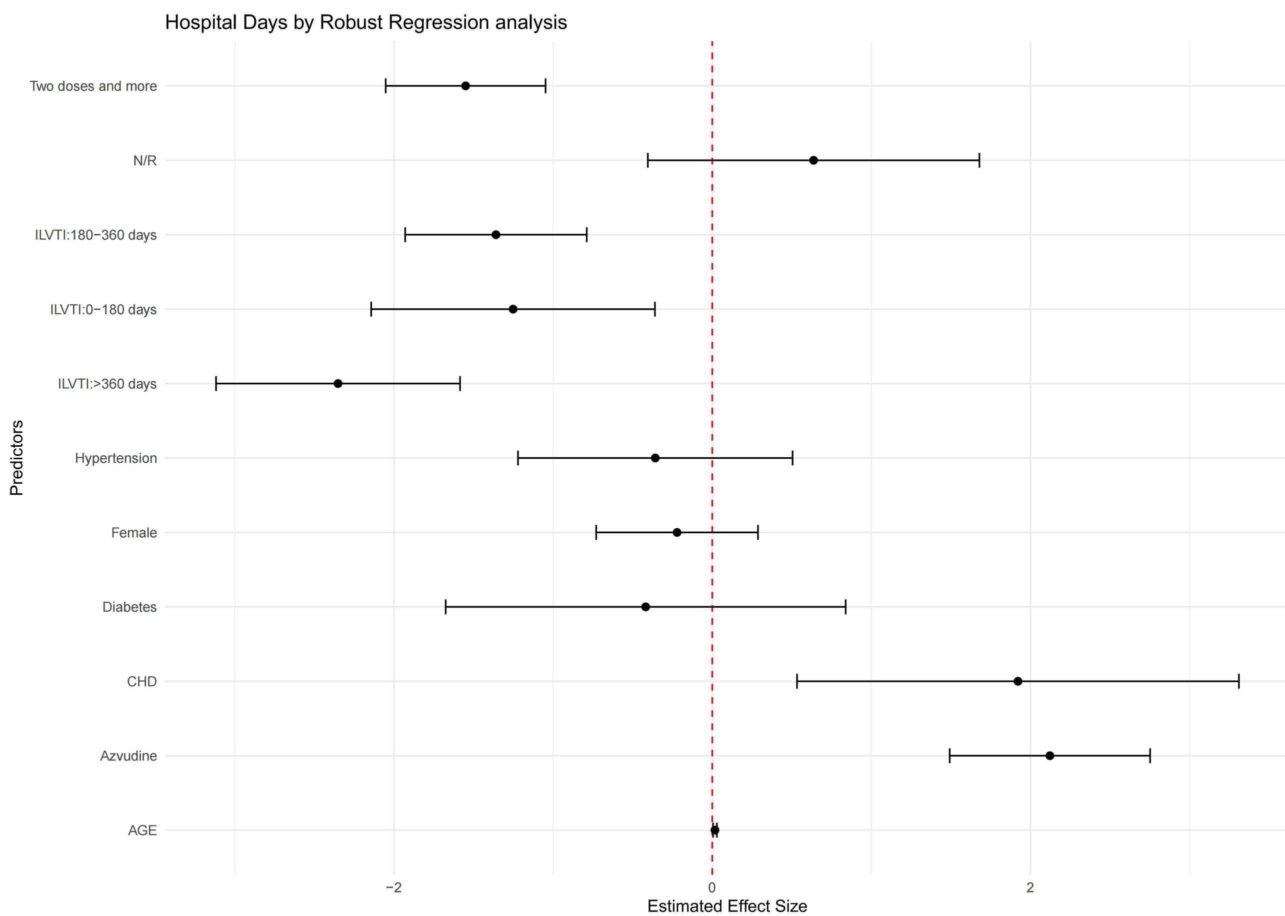

Figure 9 Influence of factors on Hospital days based on robust regression analysis.

Table 6 Hospital Days by Robust Regression Analysis

		Coefficients [95% CI]	P
Antivirus	Azvudine	2.12[1.49, 2.75]	<0.001
	N/R	0.64[−0.41, 1.68]	0.2309
Vaccination	2–3 doses	−1.55[−2.05, −1.05]	<0.001
ILVTI (≥2 doses)	0–180 days	−1.25[−2.14, −0.36]	0.006
	180–360 days	−1.36[−1.93, −0.79]	<0.001
	>360 days	−2.35[−3.12,−1.58]	<0.001
Gender	Female	−0.22[−0.73, 0.29]	0.394
Age		0.02[0.01,0.03]	0.005
Comorbidities	Hypertension	−0.36[−1.22, 0.51]	0.416
	CHD	1.92[0.53, 3.31]	0.007
	Diabetes	−0.42[−1.68, 0.84]	0.514

Discussion

This multicenter retrospective cohort study is among the first to evaluate real-world SARS-CoV-2 viral clearance kinetics in hospitalized patients during the Omicron BA.5.1.3 wave in China, focusing on the impact of inactivated vaccination schedules and antiviral therapy. Three key findings emerged: (1) ≥2 doses of inactivated vaccines spaced ≥360 days apart were associated with higher baseline Ct values, faster viral negativity, and shorter hospitalization; (2) Delayed viral clearance was independently associated with advanced age, male sex, comorbidities, and ICU admission; (3) Early Nirmatrelvir/Ritonavir use enhanced viral clearance more effectively than Azvudine or no therapy. Patients vaccinated ≥360 days prior showed the best outcomes, supporting durable immune memory and the need for frequent boosters.

Inactivated vaccines, as the primary strategy in China, provided clear protection by reducing viral loads and hospital stays. Patients vaccinated over 360 days prior to hospitalization showed the highest Ct values and fastest viral clearance, implying prolonged immune efficacy. This novel observation implies that the immunity induced by whole-virus inactivated vaccines may have greater durability, supporting a less frequent booster schedule for populations.[16–20]

Our results complement earlier reports showing that mRNA vaccines reduce severity over short intervals,[21,22] while inactivated vaccines maintain efficacy up to 20 weeks.[23–25] We extend this understanding by demonstrating beneficial effects at >360 days, providing rare long-term immunogenicity data in real-world hospitalized settings. Immunologically, inactivated vaccines present the full viral proteome, stimulating broader epitope recognition and supporting T follicular helper cell–mediated memory.[26,27] This may explain enhanced protection seen with longer intervals, and highlights the value of diversified antigenic stimulation in durable immunity.

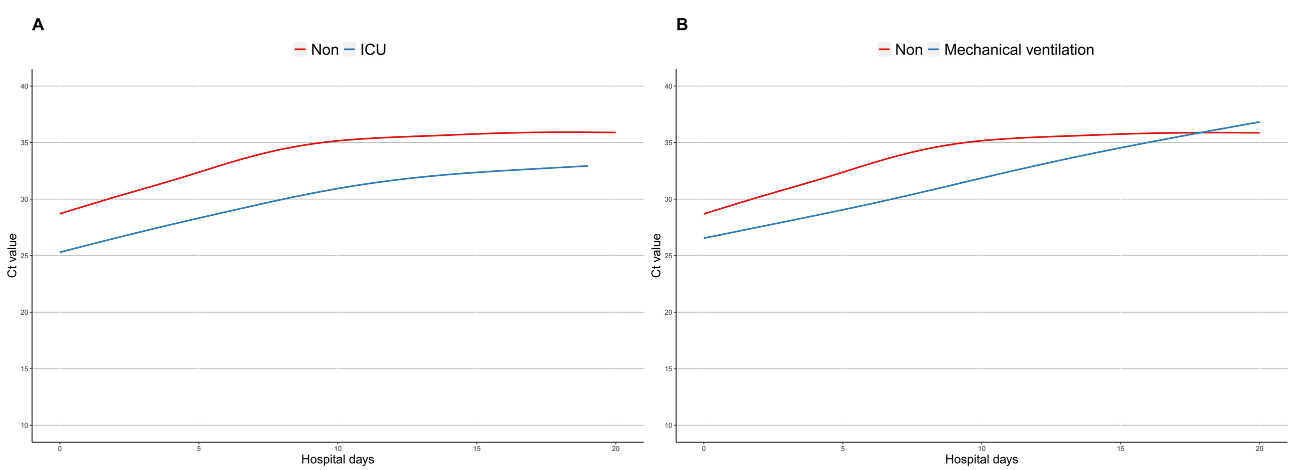

Figure 10 Comparsion between ICU vs no-ICU and MV vs no-MV on viral clearance. (**A**) Dynamic median Ct values comparing patients requiring ICU care vs those not requiring ICU care. (**B**) Median Ct values comparing patients requiring mechanical ventilation vs those not requiring ventilation.

Consistent with previous evidence, ICU patients had lower baseline Ct values and slower viral clearance, reaffirming Ct as a prognostic marker of severity and transmissibility.[28–30] Patients requiring mechanical ventilation showed similar trends, reinforcing the need for early viral suppression strategies in high-risk groups.

Among antivirals, Nirmatrelvir/Ritonavir (N/R) was more effective than Azvudine in improving viral clearance metrics, especially in patients with higher initial viral loads. Although NAT-treated patients reached viral negativity faster in some comparisons, the rate of Ct rise was highest in the N/R group, indicating stronger antiviral activity.[31–33] These findings support early targeted antiviral use, particularly in elderly or comorbid individuals.[34]

Comorbidities such as CHD, hypertension, and advanced age delayed viral clearance, likely via mechanisms of immune senescence and persistent inflammation.[35,36] Upregulated ACE2 expression in cardiovascular tissues may facilitate enhanced viral replication, prolonging viral shedding.[37–43]

In contrast, pediatric and young adult patients had faster viral clearance, consistent with lower ACE2 expression and more robust adaptive responses.[41,44–47] Age-related reductions in interferon-γ, IL-2, and memory B cell quality further explain impaired clearance in the elderly.[48,49]

This study has several limitations. Data were collected during China's zero-COVID policy, potentially limiting generalizability. Residual confounding may persist due to unmeasured variables such as healthcare access and diagnostic delays. Selection bias is possible due to unequal antiviral availability. Additionally, patients with immunosuppressive comorbidities were excluded, narrowing external validity. Lastly, the absence of post-vaccine antibody titers precludes direct immunological correlation.

In conclusion, this study demonstrates that viral clearance among hospitalized COVID-19 patients is strongly shaped by vaccination interval, antiviral strategy, and host risk profile. Receipt of ≥2 doses of inactivated vaccines spaced ≥360 days apart was associated with lower viral load and improved clinical outcomes. Moreover, early N/R treatment enhanced viral suppression in high-risk groups. These findings support a precision-medicine strategy integrating vaccination schedules and antiviral timing to optimize outcomes.

Data Sharing Statement

The data supporting the findings of this study are available in the manuscript. Further requests might require ethical approval and should be made to the corresponding authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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