Original Article

Effectiveness of Paxlovid in the treatment of the SARS-CoV-2 Omicron variant infection in children with hematologic malignancies: a retrospective cohort study

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Background: Patients with hematologic malignancies (HMs) may be immunocompromised after receiving anti-tumor therapy. Those who also have the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection face many challenges, including a lack of effective antiviral drugs. This study aimed to investigate the clinical features of the SARS-CoV-2 Omicron variant infection in children with HMs, and the effectiveness of Paxlovid.

Methods: A retrospective, non-randomized study was conducted on pediatric patients with HMs infected with the SARS-CoV-2 Omicron variant who had been admitted to the Shanghai Children's Medical Center, Shanghai, China from December 1, 2022 to March 1, 2023. The Paxlovid-treated group (Group P) comprised 21 patients, and the non-Paxlovid-treated group (Group N) comprised 21 patients. The patients' demographic data, clinical features, and therapeutic outcomes were collected. Statistical tests were used to evaluate the effectiveness of the treatment and related factors.

Results: The clinical course of the SARS-CoV-2 Omicron variant infection for most of the children with HMs was non-severe (97.6%), and only one child progressed to severe disease (2.4%). The most common symptoms were fever (66.7%) and cough (52.4%). Compared with the children in Group N, those in Group P had worse clinical characteristics, including those who previously underwent hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T (CAR-T) cell treatment (71.4% *vs.* 28.6%, P=0.005), and those in the myelosuppressive phase (57.1% *vs.* 4.8%, P<0.001). Most of the children in Group P were treated with more than two types of antibiotics (76.2% *vs.* 42.9%, P=0.02). The patients treated with Paxlovid within 5 days of diagnosis had a median viral clearance time of 5 days [interquartile range (IQR), 4–8 days], which was significantly shorter than that of the patients who were not treated with Paxlovid (P=0.03). There were no significant differences in the clinical outcomes between the two groups after the propensity score matching (PSM) analyses. Eight patients (19%) had repeat-positive (re-positive) test results. No factor was found to be statistically significant in predicting re-positive test results based on the binary logistic regression analysis.

Conclusions: Administering Paxlovid within 5 days of the diagnosis of the SARS-CoV-2 Omicron variant infection in children may effectively shorten the clearance time of the virus, but there is still the possibility the patients may have re-positive test results.

Keywords: Children; hematologic malignancies (HMs); Paxlovid; repeat-positive; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has rapidly swept the world since its discovery in December 2019, and constantly adapts to the host, evolving into new variants during replication. From December 2022 to March 2023, the effective sequences of the SARS-CoV-2 genome in China were all omicron variants, and the main epidemic strains were BA.5.2.48 and BF.7.14 (1). These strains are characterized by fast transmission, relatively mild symptoms, strong immune evasion ability, and strong concealment. Compared to healthy children, patients with hematologic malignancies (HMs) are more susceptible to COVID-19 and have a higher risk of developing severe disease after infection, as they are immunocompromised after cancer treatment (2). According to previous research, COVID-19-affected children with HMs experience continuous virus shedding and are at risk of testing nucleic acid repeat-positive (re-positive) (3,4). In disease treatment, long-term viral shedding and re-positive lead to treatment delay are accompanied by the risk of HM progression and recurrence. When children with HMs are infected with SARS-CoV-2 infection, it is necessary to balance chemotherapy strategies and consider the use of antiviral medications.

Paxlovid is a combination package of nirmatrelvir, a novel SARS-CoV-2 main protease inhibitor targeting the 3CLpro of SARS-CoV-2, plus ritonavir, which acts as an inhibitor of cytochrome P4503A4 to decrease nirmatrelvir metabolism, and increase its serum levels (5). Paxlovid is recommended for patients with non-severe COVID-19 who are at higher risk of developing severe disease or of requiring hospitalization, such as unvaccinated, older, or immunosuppressed patients (6). Paxlovid can significantly reduce the incidence and mortality of severe COVID-19 (7). The indications for Paxlovid in children are expanding based on ongoing phase 2/3 clinical trials (8). Due to the special immunocompromised status of children with HMs, more aggressive antiviral therapy should be pursued in those infected with SARS-CoV-2. In this study, we retrospectively analyzed the clinical characteristics of children with HMs infected with Omicron who were admitted to Shanghai Children's Medical Center. We also examined the therapeutic effects of Paxlovid and of increasing the medication experience of Paxlovid in children with HMs. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-70/rc).

Highlight box

Key findings

- Paxlovid shortens the virus clearance time in children with hematologic malignancies (HMs) with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant infection, but these patients may have repeat-positive (re-positive) test results.
- The neutrophil count is positively correlated with the time it takes for viral nucleic acid to turn negative.

What is known, and what is new?

- Studies with adults have shown that Paxlovid significantly reduces hospital admissions and deaths among people with coronavirus disease 2019 who are at high risk of severe illness.
- Administering Paxlovid within five days of the diagnosis of the SARS-CoV-2 Omicron variant infection in children may effectively shorten the clearance time of the virus, but patients may still test re-positive.

What is the implication, and what should change now?

- Paxlovid is recommended for children with HMs infected with SARS-CoV-2, particularly those who have undergone prior hematopoietic stem cell transplantation or chimeric antigen receptor T cell therapy.

Methods

Study population

In this single-center, retrospective study, we collected the data of 125 children with HMs combined with SARS-CoV-2 infection admitted to the Shanghai Children's Medical Center from December 1, 2022 to March 1, 2023. Among the children, 68 with incomplete clinical information, nine with a nucleic acid cycle threshold (Ct) value ≥35 at the time of diagnosis, and six who were administered Paxlovid more than 5 days after their first positive nucleic acid test results were excluded from the

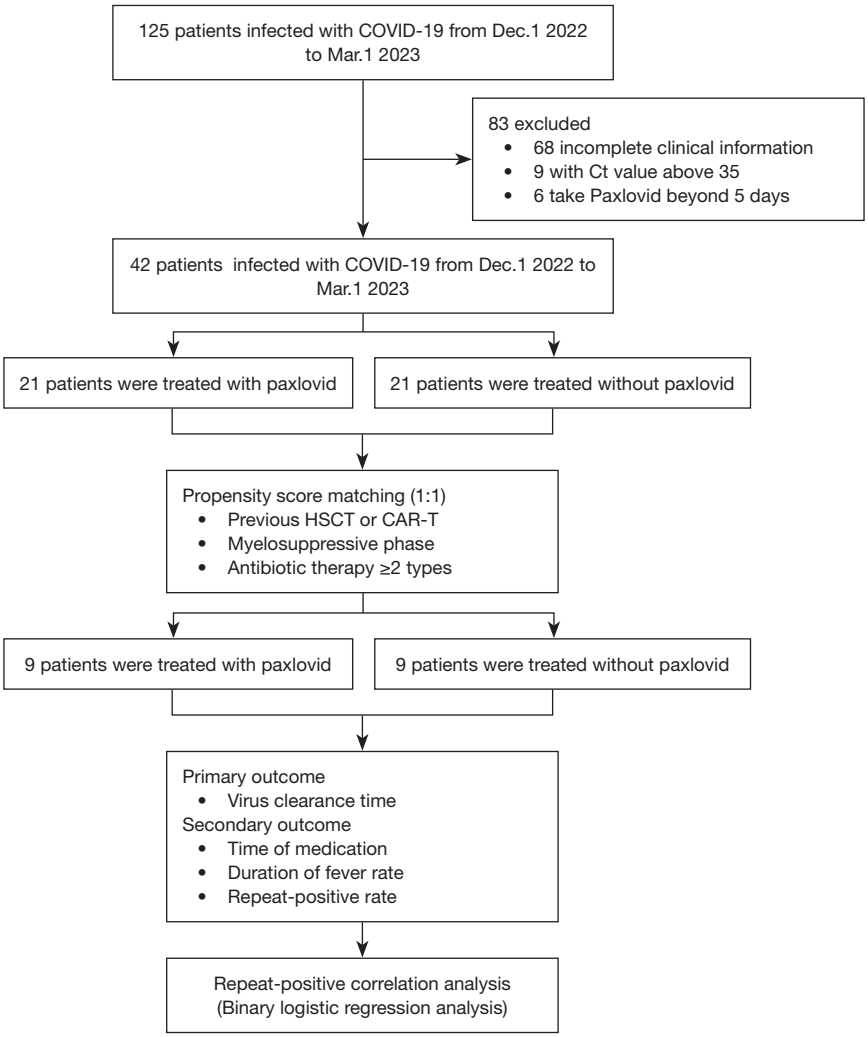

Figure 1 Research flowchart. COVID-19, coronavirus disease 2019; Ct, cycle threshold; HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T cell therapy.

study. All the remaining children were diagnosed with and treated for HMs, including non-neoplastic blood diseases, such as aplastic anemia, hematologic malignant tumors, such as leukemia and lymphoma, and other solid tumors, at the Shanghai Children's Medical Center. These patients had positive nucleic acid test results for SARS-CoV-2 in nasopharyngeal swabs and/or oropharyngeal swabs with a nucleic acid ORF1a/b (encoding RNA-dependent RNA polymerase) or N (encoding nucleocapsid protein) gene Ct value <35. Using the cohort study method, the observation endpoint was set as the nucleic acid follow up in outpatients or inpatients within 1 month of testing negative for the SARS-CoV-2 nucleic acid test. The other observation endpoints included testing negative after testing re-positive, abandoning treatment, and all-cause death. The final analysis included 42 patients, of whom 21 used Paxlovid and were categorized as the Paxlovid-treated group (Group P), and 21 did not use Paxlovid and were categorized as the control group (Group N). A flow chart of the research method is shown in *Figure 1*.

Considerations for Paxlovid treatment

Based on the hospital's policy at the time, children eligible for Paxlovid treatment had to exhibit one of the following three risk factors for progression to severe disease: (I) have an underlying disease that was relapsing or progressing; or (II) have received chemotherapy, hematopoietic stem cell

transplantation (HSCT), or chimeric antigen receptor T (CAR-T) cell treatment, and be in the myelosuppressive phase; or (III) have lung imaging demonstrating pneumonia. The children who were not treated with Paxlovid either did not fit the treatment criteria or declined to receive the medication.

Paxlovid dosage

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Medical Ethics Committee of the Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine approved the use of the clinical data and data on the use of the Paxlovid drug in children who tested SARS-CoV-2 nucleic acid positive in this study (IRB No. SCMCIRB-K2024110-1). Each child and/or their guardians signed the informed consent form for the study and the use of the Paxlovid medication. Children aged 12–14 years who weighed >40 kg were given Paxlovid (nirmatrelvir/ritonavir) 300 mg/100 mg orally twice a day, those aged 6–12 years who weighed 20–40 kg were given 150 mg/100 mg twice a day, and those aged less than 6 years who weighed <20 kg were given 150 mg/50 mg twice a day.

SARS-CoV-2 nucleic acid detection

Nasal swabs or throat swabs were sampled for the virus nucleic acid test. Two SARS-CoV-2 genes (i.e., the *ORF1a/b* and *N* genes) were simultaneously tested, and the Ct of 43 was set as the cut-off value for SARS-CoV-2 detection.

Clinical data collection

Electronic medical records were reviewed to obtain patients' demographic and clinical data, including data on gender, age, disease classification, laboratory results, chest radiographic findings, COVID-19 severity classification, clinical symptoms, and medication records. In the polymerase chain reaction tests for both the *ORF1a/b* and *N* genes, a Ct value ≥35 was considered a negative test result for SARS-CoV-2 infection, and a Ct value <35 was considered a positive test result. Two consecutive negative nucleic acid test results with an interval >24 hours, or one nucleic acid test result combined with one antigen negative test result were defined as test results that turned negative. Re-positive was defined as a nucleic acid test result that tested re-positive within 1 month after its conversion to negative. After diagnosis, the children were sampled according to the improvement of their symptoms (and were not sampled daily). The laboratory tests used the most recent blood count available at the time to confirm the diagnosis. Imaging included chest X-ray or chest computed tomography (CT) scans with the earliest confirmed diagnosis. The detection methods for pathogenic infection included blood cultures, sputum cultures, throat swabs of respiratory pathogens, or pathogenic next-generation sequencing.

Diagnostic criteria

According to the Chinese Health Commission's Novel Coronavirus Pneumonia Diagnosis and Treatment Program (version 10), the severity of infection was divided into the following four levels: mild, moderate, severe, and critical (9).

Statistical analysis

SPSS version 25.0 and GraphPad Prism version 8.3 were used for the data processing and analysis. The normally distributed variables are presented as the mean ± standard deviation, and between-group comparisons were conducted using the *t*-test. The non-normally distributed variables are presented as the median and interquartile range (IQR), and group comparisons were performed using the Wilcoxon rank-sum test. The categorical variables are presented as the number with the percentage, and between-group comparisons were carried out using the χ^2 or Fisher's exact test. Patients were matched using the propensity score matching (PSM) method at a 1:1 ratio, and variables with baseline differences were incorporated into the model for the propensity score calculation. The relationship between the length of viral clearance time and the potential influencing factors was assessed using simple linear regression, while binary logistic regression was employed to analyze the factors influencing re-positivity. All the analyses were two-sided, with statistical significance defined as $P<0.05$.

Results

Clinical characteristics

A total of 42 children with HMs and the SARS-CoV-2 infection were enrolled in the study, of whom 21 were treated with Paxlovid (Group P), and 21 were not treated

with Paxlovid (Group N). Among them, 69% had leukemia (15 in Group P, and 14 in Group N), 14.3% had lymphoma, 7.1% had other solid tumors (medulloblastoma, hepatoblastoma, and Wilms tumor), and 9.5% had aplastic anemia. Additionally, 20 patients (47.6%) had been vaccinated against COVID-19, most of whom had received two doses of vaccination. There were significant differences in the clinical features between the patients in Groups P and N. Most of the patients in Group P received HSCT or CAR-T cell therapy after being diagnosed with a HM (71.4%, P=0.005), or were in the myelosuppressive phase (57.1%, P<0.001) when infected with SARS-CoV-2, and their anti-infective therapy included more than two types of antibiotics (76.2%, P=0.02). After the SARS-CoV-2 infection, most children had fever (66.7%) and cough (52.4%) as the main symptoms, while other symptoms, such as vomiting, diarrhea, rash, headache, and chest tightness, were rare. Only 1 (2.4%) child progressed to severe disease, and most of the children had mild or moderate infections. In terms of the laboratory indicators, the routine blood results of the children in Group P were generally lower than those of those in Group N. C-reactive protein was higher in Group P than Group N, $CD4^+$ T cells were lower in Group P than Group N, and more patients had pneumonia in Group P than Group N; however, these differences were not statistically significant. Among all patients, 8 (19%) tested repeatedly positive within 1 month of the nucleic acid conversion during SARS-CoV-2 infection. There was no significant difference in the patients who tested repeatedly positive between these two groups (*Table 1*).

PSM analysis of Paxlovid effectiveness and the virus clearance time

During the monitoring of the drug, no liver or kidney function impairment, gastrointestinal intolerance, or other serious adverse effects were observed. The clinical symptoms related to COVID-19 were all alleviated in the children who used Paxlovid in this study. Specifically, the children with fever improved within 1–6 days of medication initiation. At the follow up, eight of the 12 children (66.7%) with pneumonia had their lung imaging evaluated, and the results showed remarkable recovery. In terms of the virus clearance times, the median time of 5 (IQR, 4–8) days in Group P was shorter than that of 9 (IQR, 5–10.5) days in Group N (*Figure 2*), and the difference was statistically significant (P=0.03). In this study, factors such as previous HSCT or CAR-T cell therapy, the myelosuppressive phase, and two or more types of antibiotic therapy were included in the PSM. Following the PSM, no statistically significant differences in the baseline clinical data were observed between the nine patients in Group P and the nine patients in Group N (P>0.05), and the median time of virus clearance was 7 (IQR, 4–9) days in Group P, and 6 (IQR, 4–11) days in Group N (P=0.71) (*Table 2*).

Linear regression analysis of the factors influencing the virus clearance time

To further explore the factors influencing the viral clearance time, the simple linear regression method was used to analyze the correlation between the viral nucleic acid negative time and various factors. The results showed that age, gender, vaccination status, COVID-19 severity, severity of the underlying condition, the myelosuppressive period, co-infection, and anti-infective therapy, including two or more types of antibiotics, were not significantly related to the viral clearance time. However, first neutrophil count at diagnosis was positively correlated with the time the results took to turn negative (B=0.863, P=0.02). A linear regression plot was constructed (*Figure 3*).

Binary logistic regression analysis of the risk factors for testing re-positive after the viral nucleic acid turns negative

Of the children, eight of the 42 patients tested re-positive. In Group P, five patients tested re-positive, of whom three received a second course of Paxlovid treatment due to clinical symptoms and poor underlying disease status. Among the three patients who received a second course of Paxlovid, one with concurrent multiple pathogen infections developed airway compression due to the progression of a primary neck lymphoma, requiring mechanical ventilation in the intensive care unit (ICU). The time from testing re-positive to negative conversion was 19 days. One patient tested virus re-positive after CAR-T cell therapy, leading to systemic inflammatory response syndrome, admission to the ICU, and a virus clearance time of 13 days. Another patient tested re-positive after chemotherapy, presented with cough and sputum symptoms, and had a time to negative conversion of 4 days. The remaining two re-positive cases in Group P were asymptomatic. Among the Group N patients, all three re-positive cases were asymptomatic and did not require specific treatment.

More patients tested re-positive in Group P than Group

Table 1 Clinical features of COVID-19 infection in children with hematologic malignancies

Characteristics	Total (n=42)	Group P (n=21)	Group N (n=21)	P value
Population characteristics and underlying conditions				
Gender (male)	28 (66.7)	16 (76.2)	12 (57.1)	0.19
Age (years)	8.46 [4.54, 12.16]	9.58 [6.12, 13.07]	6.5 [2.45, 11.08]	0.056
Weight (kg)	28.82 [19.42, 38.8]	30.9 [20.15, 48.2]	24 [14.9, 36.62]	0.32
Dose of vacation	20 (47.6)	10 (47.6)	10 (47.6)	>0.99
1 dose	1 (2.4)	1 (4.8)	0	>0.99
2 doses	19 (45.2)	9 (42.9)	10 (47.6)	0.75
Disease classification				
Leukemia	29 (69.0)	15 (71.4)	14 (66.7)	0.73
Lymphoma	6 (14.3)	3 (14.3)	3 (14.3)	>0.99
Other solid tumors	3 (7.1)	0	3 (14.3)	0.23
Aplastic anemia	4 (9.5)	3 (14.3)	1 (4.8)	0.59
Primary disease relapses or progresses	19 (45.2)	12 (57.1)	7 (33.3)	0.12
Previous HSCT or CAR-T	21 (50.0)	15 (71.4)	6 (28.6)	0.005
Myelosuppressive phase	13 (31.0)	12 (57.1)	1 (4.8)	<0.001
Clinical features of COVID-19				
COVID-19 symptoms				
Fever	28 (66.7)	17 (81.0)	11 (52.4)	0.08
Cough	22 (52.4)	13 (61.9)	9 (42.9)	0.21
Others	9 (21.4)	6 (28.6)	3 (14.3)	0.45
Asymptomatic	8 (19.0)	2 (9.5)	6 (28.6)	0.23
COVID-19 severity				
Mild	25 (59.5)	10 (47.6)	15 (71.4)	0.11
Moderate	16 (38.1)	10 (47.6)	6 (28.6)	0.20
Severe	1 (2.4)	1 (4.8)	0	>0.99
Laboratory examination				
White blood cell count ($\times10^9$/L)	1.83 [1.14, 3.31]	1.37 [0.61, 2.75]	2.62 [1.4, 4.62]	0.047
Neutrophil count ($\times10^9$/L)	0.64 [0.22, 1.14]	0.51 [0.03, 1.03]	1.22 [0.46, 1.69]	0.03
Lymphocyte count ($\times10^9$/L)	0.55 [0.29, 1.09]	0.36 [0.16, 0.98]	0.63 [0.36, 1.23]	0.17
Platelet count ($\times10^9$/L)	93.50 [30.75, 152.25]	64 [23, 140.5]	117 [38, 117.5]	0.22
Hemoglobin (g/L)	83.00 [65.25, 105.25]	80 [61.5, 103]	83 [71, 109]	0.52
Nucleic ORF1a/b Ct value (cycle)	31.88 [28.08, 33.30]	32.43 [27.91, 33.5]	31.65 [28.03, 33.16]	0.84
C-reactive protein (mg/L)	20.90 [2.80, 97.60]	37.1 [5.05, 118.35]	14.2 [1.97, 35.02]	0.12
$CD4^+$ T cell count (/μL)	142.41 [87.65, 333.04]	139.57 [39.15, 243.52]	170.39 [91.67, 389.79]	0.29

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Total (n=42)	Group P (n=21)	Group N (n=21)	P value
Lung imaging has inflammation	21 (50.0)	12 (57.1)	9 (42.9)	0.35
Co-infection	11 (26.2)	7 (33.3)	4 (19.0)	0.29
Antibiotic therapy ≥2 types	25 (59.5)	16 (76.2)	9 (42.9)	0.02
Time to the first viral elimination (days)	7 [4.75, 10]	5 [4, 8]	9 [5, 10.5]	0.03
Repeat-positive patient	8 (19.0)	5 (23.8)	3 (14.3)	0.69

Data are presented as n (%) or median [IQR]. Group P: Paxlovid was administered at the onset of COVID-19; Group N: Paxlovid was not administered at the onset of COVID-19. COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T cell therapy; others, vomit/diarrhea/chest tightness/hypoxemia/headache/rash; ORF1a/b, encoding RNA-dependent RNA polymerase; Ct, cycle threshold; co-infection, combine clear pathogenic infection; IQR, interquartile range.

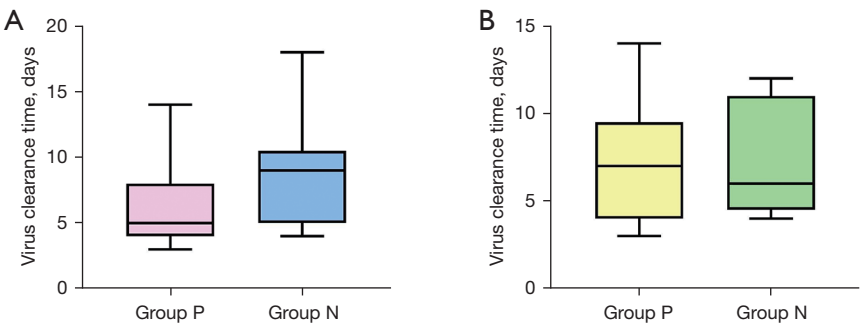

Figure 2 Time to viral clearance before and after the propensity score matching analysis. (A) Virus clearance time before propensity score matching; (B) virus clearance time after propensity score matching. Group P: Paxlovid was administered at the onset of COVID-19; Group N: Paxlovid was not administered at the onset of COVID-19. COVID-19, coronavirus disease 2019.

N, but the difference was not statistically significant (23.8% *vs.* 14.3%, P=0.69) (*Table 1*). The following risk factors were included in the binary logistic regression analysis: virological rebound after the viral nucleic acid test results turned negative, age, COVID-19 vaccination, previous HSCT or CAR-T cell therapy, the myelosuppressive phase, the nucleic acid Ct value, lung inflammatory changes, Paxlovid treatment (yes/no), and combined pathogenic infection (*Table 3*). None of these factors was found to predict whether the patients would test re-positive in this study (P>0.05).

Discussion

Only one (2.4%) of the children in this study progressed to severe disease; most of the children had mild (59.5%) and moderate (38.1%) disease; thus, most of the symptoms of the SARS-CoV-2-infected children with HMs were mild and non-severe. Fever (66.7%) and cough (52.4 %) were the most common symptoms, which is consistent with a cohort report of 131 children with tumors (10). Compared with the children in Group N, those in Group P had worse basic conditions, including previous HSCT or CAR-T cell treatment, were in the myelosuppressive phase when infected with the SARS-CoV-2, and most required more than two types of antibiotics. These statistical differences were due to the fact that the indication for the medication is to select children who are in a state of severe disease or who have high-risk factors for progression, and the purpose of this study was to explore the effectiveness and safety of Paxlovid in such children.

In this study, 20 patients (47.6%) had received the COVID-19 vaccine, but the COVID-19 vaccine was not found to have any effect on the virus clearance time. First, this result might be related to the low vaccination rates, as most of the children had received treatment or had not been vaccinated due to disease status restrictions. Second, HM patients also have a low seroconversion

Table 2 Comparison of the groups after propensity score matching

Characteristics	Group P (n=9)	Group N (n=9)	P value
Population characteristics and underlying conditions			
Gender (male)	8 (88.9)	5 (55.6)	0.29
Age (years)	9.58 [4.20, 14.5]	9.33 [2.45, 11.7]	0.56
Weight (kg)	30.9 [15.85, 59]	30.7 [15.77, 46.00]	0.93
Inactivated COVID-19 vaccine	7 (77.8)	5 (55.6)	0.62
Primary disease relapses or progresses	6 (66.7)	6 (66.7)	>0.99
Previous HSCT or CAR-T	6 (66.7)	6 (66.7)	>0.99
Myelosuppressive phase	1 (11.1)	1 (11.1)	>0.99
Clinical features of COVID-19			
COVID-19 severity			
Mild	4 (44.4)	8 (88.9)	0.13
Moderate	4 (44.4)	1 (11.1)	0.29
Severe	1 (11.1)	0	>0.99
Laboratory examination			
White blood cell count ($\times10^9$/L)	3.19 [1.62, 4.16]	3.09 [1.07, 5.02]	>0.99
Neutrophil count ($\times10^9$/L)	0.64 [0.41, 2.62]	1.24 [0.37, 2.46]	0.95
Lymphocyte count ($\times10^9$/L)	0.49 [0.31, 1.59]	1.16 [0.36, 1.39]	0.56
Platelet count ($\times10^9$/L)	119 [83.5, 214]	106 [32.5, 141]	0.25
Hemoglobin (g/L)	99 [82, 119]	104 [74.5, 109]	0.50
Nucleic ORF1a/b Ct value (cycle)	32.77 [26.86, 33.92]	32.85 [29.98, 33.7]	0.75
C-reactive protein (mg/L)	20 [2.3, 67.35]	21.15 [1.32, 49.27]	0.83
$CD4^+$ T cell count (/μL)	150.20 [71.23, 328.17]	283.81 [128.72, 576.04]	0.22
Lung imaging has inflammation	5 (55.6)	3 (33.3)	0.63
Co-infection	5 (55.6)	4 (44.4)	>0.99
Antibiotic therapy ≥2 types	6 (66.7)	6 (66.7)	>0.99
Time to the first viral elimination (days)	7 [4, 9]	6 [4, 11]	0.71
Repeat-positive patient	1 (11.1)	1 (11.1)	>0.99

Data are presented as n (%) or median [IQR]. Group P: Paxlovid was administered at the onset of COVID-19; Group N: Paxlovid was not administered at the onset of COVID-19. COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T cell therapy; ORF1a/b, encoding RNA-dependent RNA polymerase; Ct, cycle threshold; co-infection, combine clear pathogenic infection; IQR, interquartile range.

rate after vaccination, especially under several treatment regimens (11). The children included in this study had only received up to two doses of the COVID-19 vaccine. However, research has shown that administering additional vaccine doses to cancer patients who do not exhibit a full immune response following two doses of the COVID-19 messenger ribonucleic acid vaccine can boost their humoral immune response and offer protection against emerging variants of the virus (12). Breakthrough infections can also occur in fully vaccinated patients with HMs and may be associated with a serious prognosis (13,14). There are still some guidelines for the vaccination of children with

hematological cancers, such as the United States (US) National Comprehensive Cancer Network (NCCN) guidelines (15) and the European Conference on Infections in Leukemia (ECIL 9) guidelines (16), which propose that vaccination strategies for different HM patients can further improve the vaccination process and bring benefits to children with HMs.

The youngest child who used Paxlovid in this study was 19 months old and weighed 11 kg, which is the youngest age of any child who has been reported to receive Paxlovid to date. The child had obvious fever and cough symptoms at the time of admission, and soon progressed to severe COVID-19 pneumonia and needed oxygen support. Paxlovid is a combination package of nirmatrelvir tablets combined with viral protease enhancer ritonavir tablets. The US Food and Drug Administration has authorized the use of Paxlovid, which includes nirmatrelvir and ritonavir, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients >12 years of age and weighing at least 40 kg with positive results of direct SARS-CoV-2 (17). The results of five children aged 6–14 years old with basic diseases and COVID-19 successfully turned negative after using Paxlovid (18). The results of nine children with tumors have also been reported to have successfully turned negative after treatment with Paxlovid, the youngest of whom was 4 years old and weighs 18 kg (19). These patients responded well after using Paxlovid, which provides a feasible basis for the use of Paxlovid in young age groups.

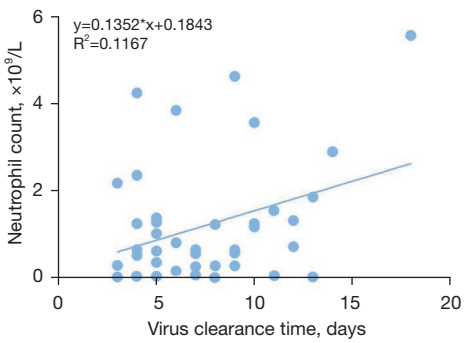

Figure 3 Simple linear regression suggested that the neutrophil count was positively correlated with the viral clearance time.

Ritonavir acting as a pharmacokinetic (PK) enhancer of nirmatrelvir increases the systemic concentrations and half-lives of nirmatrelvir. The PK of Paxlovid in adults showed a T_{max} at 3 h versus a $T_{1/2}$ at about 6 h. Single doses can reach up to 750 mg, and multiple doses can reach up to 500 mg daily. In the package nsert, it was administered twice daily for 5 days and reached a steady state on the Day 2, accumulating approximately two-fold (17). The PK/pharmacodynamics (PD) of Paxlovid in children is unknown, and professional clinical pharmacists provide possible effective and safe doses based on their experience of PK/PD in children. In this study, PK/PD was not evaluated after pediatric medication, and more studies are needed to explore the effective dose and time of Paxlovid use in children of different ages. No adverse effects were observed in the clinical observation of all the patients.

The median time it took for the virus to turn negative among the 42 children in this cohort was 7 (IQR, 4.75–10) days. The Paxlovid instructions emphasize that it should be used

Table 3 Binary logistic regression analysis of the factors influencing repeat-positive test results

Impact factors	B value	OR	95% CI	P value
Age	–0.22	0.802	0.601–1.071	0.13
Inactivated COVID-19 vaccine	0.165	1.179	0.13–10.655	0.88
Previous HSCT or CAR-T	0.301	1.352	0.158–11.559	0.78
Myelosuppressive phase	0.898	2.455	0.318–18.952	0.38
Nucleic ORF1a/b Ct value	0.082	1.085	0.847–1.39	0.51
Lung imaging has inflammation	0.037	1.038	0.172–6.246	0.96
Administration Paxlovid	0.718	2.05	0.188–22.333	0.55
Co-infection	0.266	1.305	0.14–12.176	0.81

OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T cell therapy; ORF1a/b, encoding RNA-dependent RNA polymerase; Ct, cycle threshold; co-infection, combine clear pathogenic infection.

within 5 days of symptoms in the early stage of SARS-CoV-2 infection to achieve efficacy. The median time to viral clearance with Paxlovid within 5 days of diagnosis was 5 (IQR, 4–8) days, which was significantly shorter than that of children never took Paxlovid. More patients underwent HSCT or CAR-T cell therapy in Group P than Group N. The samples of this group of patients were lost after PSM, resulting in a negative conversion time that was meaningless. Thus, the Paxlovid may be more efficacious in patients with HMs after HSCT or CAR-T cell therapy, but this requires further study.

COVID-19 has been reported to cause a decrease in the neutrophil count, which may be a risk factor for progression to severe disease (20). Inconsistent with previous reports, the neutrophil count was positively correlated with the viral clearance time in this study. Most of the patients who used Paxlovid were in the myelosuppressive phase (57.1%); thus these results do not truly reflect the effect of SARS-CoV-2 on the neutrophil count. Since patients with HMs have abnormal complete blood counts related to their disease, the independent effect of abnormal incomplete blood cell counts on the prognosis of COVID-19 in tumor patients is still unclear.

Notably, 19% of the children in this cohort tested re-positive, but there was no significant difference in the number of patients who tested re-positive in Groups P and N. Thus, Paxlovid might not improve the occurrence of re-positive results in children with HMs. A Hong Kong study reported that the rates of viral burden rebound were similar between patients who received Paxlovid treatment and those who did not. Importantly, the rebound of viral burden was not linked to adverse clinical outcomes (21). A "rebound" phenomenon has been observed in adults treated with Paxlovid (whereby patients test re-positive after 5 days of regular drug use), but this mainly occurs in patients with underlying medical conditions, and is also not unique to Paxlovid. The independent effect of Paxlovid drug "rebound" is not clear. One study found that neither Paxlovid resistance nor a lack of neutralization immunity was a possible cause of re-positive nucleic acid test results, which were most likely caused by under-exposure or an insufficient individual PK drug duration (22). Unfortunately, our binary logistic regression analysis failed to reveal the factors associated with the re-positive test results. Three symptomatic children with re-positive results were treated again with Paxlovid, and their times to test negative were 19, 13, and 4 days, respectively. Given the limited number of cases, it was not feasible to assess the effectiveness of Paxlovid in children experiencing rebound. A clinical trial is currently in progress to assess the effectiveness of a second course of nirmatrelvir/ritonavir in the treatment of patients experiencing viral rebound and recurring symptoms (23).

The study had a number of limitations. First, as a small-size, observational study, the PSM failed to produce meaningful results. Second, as the factors influencing re-positive results and the significant extension of the virus conversion time could not be further analyzed, and viral genome sequencing was not performed, it was not possible to determine whether these re-positive patients were repeatedly infected with the same strain or other strains. Third, no PK or PD analyses were conducted in this study, thus it is difficult to know the optimal dose for children. In the future, a large-sample study of children with HMs who are treated with Paxlovid after infection with SARS-CoV-2 needs to be conducted.

Conclusions

Administering Paxlovid within 5 days of the diagnosis of the SARS-CoV-2 Omicron variant infection in children may effectively shorten the clearance time of the virus, but there is still the possibility these patients will test re-positive.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-70/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-70/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.

com/article/view/10.21037/tcr-24-70/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The use of the clinical data and the data on the use of drug Paxlovid in children who tested SARS-CoV-2 nucleic acid positive was approved by the Medical Ethics Committee of the Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine (IRB No. SCMCIRB-K2024110-1). Each child and/or their guardians signed an informed consent form for the study and consented to the use of the Paxlovid medication.

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