International Journal of Infectious Diseases 160 (2025) 108053

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Risk factors for persisting SARS-CoV-2 infection in patients with B-cell malignancies in the Omicron era: A multicenter cohort study

Zeno Pasquini[1,*], Alice Toschi[2], Dino Gibertoni[3], Armando Amicucci[2], Beatrice Casadei[2,3,4], Cinzia Pellegrini[2,3,4], Alessandra D'Abramo[5], Patrizia De Marco[5], Linda Bussini[6,7], Maria Ciccone[8], Alessandro Visentin[9], Paula Olivares-Navarro[10,11], Michele Bartoletti[6,7], Emanuele Nicastri[5], Mauro Krampera[8,12], Pier Luigi Zinzani[2,4], Francesca Bonifazi[4], Pierluigi Viale[1,2], Zaira R. Palacios-Baena[10,11], Evelina Tacconelli[9], Maddalena Giannella[1,2], ORCHESTRA study group[#]

[1] *Infectious Diseases Unit, Department for Integrated Infectious Risk Management, IRCCS AziendaOspedaliero-Universitaria di Bologna, Bologna, Italy*
[2] *Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy*
[3] *Epidemiology and Statistics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[4] *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy*
[5] *National Institute for Infectious Diseases "Lazzaro Spallanzani", IRCCS, Rome, Italy*
[6] *Infectious Disease Unit, IRCCS Humanitas Research Hospital, Milan, Italy*
[7] *Department of Biomedical Sciences, Humanitas University, Milan, Italy*
[8] *UOC di Ematologia, DAI Medico Generale, AOUI Verona, Verona, Italy*
[9] *Division of Infectious Diseases, Department of Diagnostics and Public Health, University of Verona, Verona, Italy*
[10] *Hospital Universitario Virgen Macarena, Departamento de Medicina, Universidad de Sevilla, Instituto de Biomedicina de Sevilla (IBiS)/CSIC, Seville, Spain*
[11] *CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain*
[12] *Hematology and Bone Marrow Transplant Unit, Section of Biomedicine of Innovation, Department of Engineering of Innovative Medicine (DIMI), University of Verona, Verona, Italy*

ARTICLE INFO

Article history:
Received 30 June 2025
Revised 23 August 2025
Accepted 7 September 2025

Keywords:
Persisting SARS-CoV-2 infection
B-cell malignancies
Anti-CD20 monoclonal antibody therapy
Early antiviral treatment for SARS-CoV-2
COVID-19 in hematologic patients

ABSTRACT

Objectives: Patients with B-cell malignancies are at high risk of persisting SARS-CoV-2 infection, which may delay oncologic treatments and increase morbidity. We aimed to assess risk factors for persisting infection in this population.

Methods: We conducted a multicenter retrospective study across five tertiary hospitals between January 1, 2022, and January 1, 2023. Adult patients with B-cell malignancies and SARS-CoV-2 infection were included. Persisting infection was defined as viral shedding ≥21 days with clinical and/or radiological signs. Risk factors were evaluated through multivariable logistic regression.

Results: Among 307 patients, 26.1% developed persisting infection. The cohort included non-Hodgkin lymphoma (67.4%), chronic lymphocytic leukemia (19.2%), and Hodgkin lymphoma (9.1%). Independent risk factors included anti-cluster of differentiation 20 therapy (odds ratio [OR], 3.22; 95% confidence interval [CI], 2.37-4.39; P <0.001), and hospital admission at diagnosis (OR, 5.16; 95% CI, 2.37-12.45; P <0.001). Early therapy with nirmatrelvir/ritonavir (OR, 0.32; 95% CI, 0.19-0.54; P <0.001), remdesivir (OR, 0.26; 95% CI, 0.18-0.37; P <0.001), and sotrovimab (OR, 0.32; 95% CI, 0.15-0.67; P = 0.003) were protective. Mortality at 120 days was higher in the persisting group, though not statistically significant (12.5% vs 8.4%; P = 0.277).

Conclusions: Our findings help define risk factors for persisting SARS-CoV-2 infection and support early treatment in patients with B-cell malignancies.

© 2025 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

* Corresponding author.
E-mail address: zeno.pasquini@aosp.bo.it (Z. Pasquini).

[#] ORCHESTRA study group: Lorenzo Maria Canziani, Anna Maria Azzini, Gaia Maccarrone, Lorenza Lambertenghi, Natascia Caroccia, Michela Di Chiara, Francesca Simone, Alessandro Cilli, Federica Malerba, Martina Casarini, Alberto Pecorelli, Domenico Marzolla, Andrea Volpe, Filippo Miselli, Jesus Rodriguez-Baño, Maria Giulia Caponcello, Alicia Rodriguez-Fernandez, Julia Montero Benitez, Aurora Aleman Rodriguez, Lola Cubero Aranda.

https://doi.org/10.1016/j.ijid.2025.108053
1201-9712/© 2025 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Immunocompromised hosts (ICHs) are still shown to be at higher risk compared to the general population of acquiring SARS-CoV-2 infection [1,2]. In a large observational cohort study from England on patients receiving a diagnosis of SARS-CoV-2 infection in 2023, the authors showed that despite widespread vaccination, ICHs still experience higher rates of COVID-19–related hospitalizations and mortality compared to non-immunocompromised individuals [3]. These findings highlight the ongoing clinical burden of COVID-19 in this population and emphasize the need for improved prevention and treatment strategies.

Among ICHs, those with hematologic malignancies, particularly B-cell malignancies and those receiving B-cell–depleting therapies, such as monoclonal antibodies (mAbs) targeting the cluster of differentiation 20 (CD20) antigen (anti-CD20) and chimeric antigen receptor T-cell (CAR-T) therapy, are at increased risk of prolonged viral shedding, viral rebound, and persisting infection. This subgroup represents a major clinical challenge, as persisting SARS-CoV-2 infection may not only delay life-saving oncological treatments but also increase the risk of viral subvariants emergence [4–7].

Although the definition of persisting SARS-CoV-2 infection remains heterogeneous, various studies have attempted to characterize it and assess its clinical impact [7–12]. In particular, two studies focused on differentiating this phenomenon from “long COVID-19” and “post-COVID-19 condition,” proposing diagnostic criteria that integrate baseline host immunodeficiency, clinical manifestations, and virological data [11–13]. Regarding therapeutic management, several case series have suggested combined antiviral approaches, such as dual antiviral therapy, mAbs, convalescent plasma, or prolonged antiviral regimens [14–16]. However, there is still a lack of robust data to identify patients at the highest risk for persisting infection, which could help tailor early and more aggressive therapeutic strategies.

To address this gap, we conducted a multicenter retrospective observational study to investigate the risk factors for persisting SARS-CoV-2 infection in hematologic patients with B-cell malignancies attending five tertiary hospitals in Europe. The secondary objective was to describe clinical, virological, radiological outcomes and the therapeutic management of patients with persisting infection.

Materials and methods

Study design and setting

This study is part of the EU H2020 project “Connecting European Cohorts to Increase Common and Effective Response to the SARS-CoV-2 Pandemic: ORCHESTRA”.

We conducted a retrospective observational study across five hospitals in Italy and Spain: IRCCS Azienda Ospedaliero-Universitaria of Bologna, IRCCS Istituto Clinico Humanitas of Milan, Hospital Virgen Macarena of Seville, Azienda Ospedaliera Universitaria Integrata of Verona, and IRCCS Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani of Rome. The study period was from January 1, 2022, to January 1, 2023, with a follow-up of 120 days from the initial diagnosis of SARS-CoV-2 infection. This timeframe was selected to focus on the impact of the Omicron variant and its subvariants.

Throughout the study period, screening for SARS-CoV-2 infection and its persistence, as well as therapeutic management, was performed at the discretion of the attending physicians, following local protocols and routine clinical practice.

Study population

All adult patients ($\geq$18 years) attending the participating centers as inpatients or outpatients with a new diagnosis of SARS-CoV-2 infection (index episode) during the study period were screened for inclusion. Inclusion criteria were: (i) diagnosis of B-cell malignancy or treatment with B-cell–depleting therapies; (ii) polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection (only the first infection during the study period was considered; recurrence was assessed as a secondary endpoint); and iii) provision of signed informed consent.

Endpoints and exposure variables

The primary endpoint was persisting SARS-CoV-2 infection, defined as the persistence or recurrence of clinical signs and symptoms such as fever, dyspnea, hypoxemia, or radiological changes and a persistently positive SARS-CoV-2 PCR test for $\geq$21 days following the initial positive result (index episode) [11,12].

Secondary endpoints were assessed within 120 days of the SARS-CoV-2 infection diagnosis and included: therapeutic management of persisting SARS-CoV-2 infection, including hospital admission, administered drugs and length of treatment; virological clearance and duration of viral shedding, defined as the number of days between the first positive and first negative PCR assay; clinical cure, defined as the resolution of clinical, laboratory, and radiological findings associated with SARS-CoV-2 infection; recurrence within 120 days, defined as new positive test with or without symptoms after a documented viral clearance; and all-cause mortality.

Exposure variables included demographics (age and sex), comorbidity burden according to the Charlson index, underlying hematologic malignancy (HM), time from HM diagnosis to index episode, treatment received for the HM, including hematopoietic stem cell transplantation (HSCT) and CAR-T therapy or other cell re-directing therapies, and HM status at index SARS-CoV-2 infection. For the index episode, the patient’s immune status was recorded according to naïve status, prior infection, and vaccination status, including the number of dosages and the date of last vaccine dose administration. Clinical severity of infection was recorded according to World Health Organization (WHO) criteria as mild, moderate, severe, or critical [17]. The need for hospital and intensive care unit (ICU) admission, as well as oxygen support, was also recorded. Radiological investigations and relative corresponding findings were collected. For therapeutic management, early antiviral treatment was defined as guideline–concordant therapy initiated within 5 days from index diagnosis and coded in four mutually exclusive categories: none, molnupiravir (5–day course), nirmatrelvir/ritonavir (5–day course), or remdesivir (3–day course). We also recorded exposure to long-acting anti-SARS-CoV-2 monoclonal antibodies administered within the six months prior to the index infection, and exposure to therapeutic mAbs administered within 10 days after the index SARS-CoV-2 diagnosis. In hospitalized patients, we additionally recorded other therapeutic management of the index episode.

Data management

Pseudonymized data were collected using a standardized electronic case report form (eCRF) developed with the REDCap platform, hosted by CINECA, the Italian partner responsible for data management within the EU H2020 ORCHESTRA project. Clinical charts and hospital electronic records were used as data sources.

To ensure data quality, a structured data validation plan was implemented, including integrity checks, accuracy verification, and query generation when necessary.

Statistical analysis

Participants' characteristics expressed by categorical variables were presented as absolute and relative frequencies, while continuous variables were summarized by mean and standard deviation if normally distributed or by median and interquartile range (IQR) if non-normally distributed. For group comparison, Student's *t*-test, Mann–Whitney test, and ANOVA (Analysis of Variance) or Kruskal–Wallis test were used for continuous variables, and Pearson's χ^2 test or Fisher's exact test for categorical variables, where appropriate. Shapiro–Wilk's and Kolmogorov–Smirnov tests, as well as visual methods, were applied to test for normality.

To identify the risk factors associated with persisting SARS-CoV-2 infection, a multivariable logistic regression was performed. Variables considered a priori (age and sex) and those with P <0.10 in bivariate comparisons were candidates for multivariable logistic regression. Since radiographic pneumonia and WHO severity were strongly correlated with hospitalization at diagnosis, we used hospital admission at diagnosis as the severity proxy and excluded radiographic pneumonia and WHO severity to limit collinearity. Early antiviral treatment entered the model as dummy indicators for each category (reference: none). Bendamustine exposure (≤6 months) was included in an additional model to address potential confounding by anti–CD20 co-exposure (Suppl Table 2). Subgroup analyses were conducted for the principal hematologic malignancies, non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL).

In this model, participants with missing data on hematologic treatments (n = 23) were excluded, as well as those from the Spallanzani Hospital (n = 15) due to the high rate of persisting SARS-CoV-2 infection in this center, suggestive of a selection bias in screening for persisting infection. Treatment with tixagevimab/cilgavimab was changed to absent in n = 12 participants who received it more than 10 days after or 180 days before the index episode, or if the date of administration was missing. Robust standard errors were obtained by adjusting for patients' clustering within centers. Analyses were carried out using SPSS v.28.0 and Stata v.18.5.

Results

Overall, 343 patients were deemed eligible. Of these, 12 patients were excluded due to missing data, and 24 were excluded due to underlying hematologic conditions involving the myeloid line, including 16 with acute myeloid leukemia, four with chronic myeloid leukemia, and four with myelodysplastic syndromes (Suppl Figure 1). Thus, 307 patients were included in the analysis. Distribution of patients per center is shown in Suppl Table 1. The median age was 67 years (IQR, 56–73), and 184 (59.9%) were male. The median Charlson comorbidity index was 5 (IQR, 4–6), with the most frequent comorbidities being diabetes mellitus (12%), peripheral vascular disease (11%), solid tumors (10%), and chronic obstructive pulmonary disease (8%). Distribution of hematologic malignancy, hematologic treatments, SARS-CoV-2 immune status at index infection, and antiviral treatment are shown in Table 1. At the index episode, chest radiological exams were performed in 116 patients (37.8%), with 46 undergoing chest X-ray, 63 chest CT scan, and seven undergoing both. Signs of bilateral pneumonia were observed in 65 patients (21.2%).

Early antiviral therapy distribution was as follows: none, 104/307 (33.9%); molnupiravir, 24/307 (7.8%); nirmatrelvir/ritonavir, 81/307 (26.4%); and remdesivir, 97/307 (31.6%). Sotrovimab was administered as early therapeutic monoclonal antibody in 26/307 patients (8.5%), whereas casirivimab/imdevimab and bamlanivimab/etesevimab were used only in two and one patients, respectively. Data on virological outcomes were available for 285 patients; among these, 266 (93.3%) reached virological clearance within a median of 17 days (IQR, 10–33) after index-SARS-CoV-2 infection diagnosis. Data on clinical cure were available for 302 patients; among these, 276 (91.4%) achieved symptom resolution within a median of 14 days (IQR, 7–26) from disease onset. Recurrence following a negative test was observed in 14/305 (4.6%) patients within 120 days. Overall, mortality within 120 days was 9.4% (29/307).

Overall, 80 patients were identified as having persisting SARS-CoV-2 infection, with an overall rate of 26.1%, varying by center: 16.8% in Bologna, 24.3% in Milan, 31.0% in Verona, 45.2% in Seville, and 84.2% in Rome. The median time from index episode to the diagnosis of persisting SARS-CoV-2 infection was 29 days (IQR, 22–46). Data about diagnostic sampling were available for 74 patients, of which 66 had positive nasopharyngeal swabs, four had both nasopharyngeal swabs and bronchoalveolar lavage showing persisting infection, and four had only positive bronchoalveolar lavage with negative nasopharyngeal swab. PCR cycle threshold values were available for 26 patients, with a median value of 28 (IQR, 20.75–29.25).

During persisting SARS-CoV-2 infection, 39 (48.7%) patients received treatments outside the standard of care, including 32 (82.1%) treated with remdesivir for a median of 9 days (IQR, 4–12), 24 (61.6%) with nirmatrelvir/ritonavir, 21 of whom received it in combination with remdesivir. In six patients, corticosteroids were also administered.

The comparison between patients with and without persisting SARS-CoV-2 infection according to immunization status, use of pre-exposure prophylaxis, early therapeutic management, and in-hospital treatment is shown in Table 1. Main significant differences were observed for the following variables: type of hematologic malignancy; hematologic treatments, in particular anti-CD20, Bruton tyrosine kinase inhibitors (BTKi), and CAR-T therapy; days from last vaccine administration to index diagnosis; use of tixagevimab/cilgavimab; clinical severity at diagnosis, including radiological findings, hospital admission, and need for O_2 therapy support; virological clearance; and clinical cure.

A multivariable logistic regression considering NHL as the reference hematologic disease was performed and is reported in Table 2. In the multivariable model, no hematologic malignancy was independently associated with persisting SARS-CoV-2 infection. Independent risk factors included anti-CD20 therapy (OR, 3.225; 95% CI, 2.368–4.391; P <0.001), hospital admission at the index episode (OR, 5.160; 95% CI, 2.368–12.447; P <0.001), time from hematologic malignancy diagnosis to index infection (OR, 1.008; 95% CI, 1.002–1.013; P = 0.004), and tixagevimab/cilgavimab administration (OR, 4.645; 95% CI, 1.112–19.395; P = 0.035). Early treatments with nirmatrelvir/ritonavir (OR, 0.322; 95% CI, 0.193–0.539; P <0.001), 3-day remdesivir (OR, 0.255; 95% CI, 0.176–0.370; P <0.001), and sotrovimab (OR, 0.324; 95% CI, 0.153–0.686; P = 0.003) were protective, whereas molnupiravir was not (OR, 0.544; 95% CI, 0.240–1.231; P = 0.144). (Table 2, Figure 1). In the additional model including bendamustine (≤6 months), no independent association with persistence was observed (OR, 1.144; 95% CI, 0.363–3.611; P = 0.818). (Suppl Table 2).

In subgroup analyses, NHL mirrored the overall cohort: anti-CD20 exposure and hospitalization at diagnosis were associated with increased risk of persistence, whereas early nirmatrelvir/ritonavir and 3-day remdesivir were protective (Suppl Table 3). In CLL, descriptive comparisons showed higher rates of pneumonia and hospitalization among persisting cases, but the sample size precluded robust multivariable modeling (Suppl Table 4).

Table 1
Comparison of patients with and without persisting SARS-CoV2 infection.

Characteristic	Overall N = 307 (%)	Non-persisting N = 227 (%)	Persisting N = 80 (%)	*P-value*
Age, years (median, IQR)	67 (56-73)	66 (55-73)	69 (57.25-76)	0.33
Sex				0.89
Female	123 (40.1)	90 (39.6)	33 (41.3)	
Male	184 (59.9)	137 (60.4)	47 (58.8)	
Charlson comorbidity index (median, IQR)	5 (4-6)	5 (3-6)	5 (4-6)	0.92
Type of hematologic malignancy				0.009
Non-Hodgkin lymphoma	207 (67.4)	150 (66.1)	57 (71.3)	
Chronic lymphocytic leukemia	59 (19.2)	44 (19.4)	15 (18.8)	
Hodgkin lymphoma	28 (9.1)	27 (11.9)	1 (1.3)	
Multiple myeloma	8 (2.6)	3 (1.3)	5 (6.3)	
Acute lymphocytic leukemia	5 (1.6)	3 (1.3)	3 (2.5)	
Months from HM diagnosis to index episode (median, IQR)	25 (8-74)	22 (7-70)	33 (12.5-78.2)	0.41
(missing)	*2*	*0*	*2*	
Treatment for underlying condition				
Anti-clusters of differentiations 20	165/285 (57.9)	109/210 (51.9)	56/75 (74.7%)	<0.001
Bendamustina	33/285 (10.7)	20/210 (8.8)	13/75 (16.2)	0.069
Bruton tyrosine kinase inhibitor	67/285 (23.5)	56/210 (26.7)	11/75 (14.7)	0.039
Number of treatment lines (median, IQR)	2 (1-3)	1 (1-2.75)	2 (1-3)	0.56
(missing)	*66*	*39*	*27*	
HSCT	29 (9.4)	23 (10.1)	6 (7.5)	0.50
Auto-HSCT	23 (7.5)	18 (7.9)	5 (6.3)	
Allo-HSCT	6 (2.0)	5 (2.2)	1 (1.3)	
Chimeric antigen receptor T-cell	18 (5.9)	9 (4.0)	9 (11.3)	0.025
Index episode features				
Immunization status				
Naïve	29 (9.4)	22 (9.7)	7 (8.8)	0.83
Prior infection	18 (5.9)	13 (5.7)	5 (6.3)	1.
Vaccination	277 (90.2)	204 (89.9)	73 (91.3)	0.82
Number of dosages (median, IQR)	3 (3-3)	3 (3-3)	3 (3-4)	0.61
Days from last dose (median, IQR)	140 (69.2-263.5)	134 (71-255)	208 (67-342)	0.05
(missing)	*57/277*	*39/204*	*18/73*	
Monoclonal antibodies				
Sotrovimab	26 (8.5)	23 (10.1)	3 (3.8)	0.078
Tixagevimab/cilgavimab use	14 (4.6)	6 (2.6)	8 (10.0)	0.007
Others[a]	3 (1.0)	3 (1.0)	0 (0.0)	0.57
Clinical severity at diagnosis				<0.001
Mild	237 (77.2)	191 (84.1)	46 (57.5)	
Moderate	57 (18.6)	29 (12.8)	28 (35.0)	
Severe	10 (3.3)	6 (2.6)	4 (5.0)	
Critical	3 (1.0)	1 (0.4)	2 (2.5)	
Radiological findings				
Bilateral pneumonia	65 (21.2)	32 (14.0)	33 (41.3)	<0.001
Need of hospital admission	73 (23.8)	36 (15.9)	37 (46.3)	<0.001
Need of intensive care unit admission	10 (3.3)	6 (2.6)	4 (5.0)	0.46
Therapeutic management of index episode				
Early treatment				0.058
None	104 (33.9)	67 (29.5)	37 (46.3)	
Remdesivir	97 (31.6)	74 (32.6)	23 (28.7)	
Nirmatrelvir/r	81 (26.4)	67 (29.5)	14 (17.5)	
Molnupiravir	24 (7.8)	18 (7.9)	6 (7.5)	
In-hospital treatment				
O2 support	31 (10.1)	14 (6.2)	17 (21.3)	<0.001
Remdesivir	21 (6.8)	12 (5.3)	9 (11.3)	0.076
Corticosteroids	18 (5.9)	10 (4.4)	8 (10.0)	0.09
Tocilizumab	8 (2.6)	4 (1.8)	4 (5.0)	0.21
Outcomes				
Virological clearance	266/285 (93.3)	205/205 (100)	61/80 (76.3)	<0.001
Days to virological clearance (median, IQR)	17 (10-33)	14 (9-20.75)	51 (37.50-88)	<0.001
(missing)	*46*	*27*	*19*	
Clinical cure	276/302 (91.4)	210/223 (94.2)	66/79 (83.5)	0.006
Recurrence within 120 days	14/305 (4.6)	7/225 (3.1)	7/80 (8.7)	0.078
Death within 120 days	29 (9.4)	19 (8.3)	10 (12.5)	0.277

IQR, interquartile range.
[a] Two patients treated with casirivimab/imdevimab and one with bamlanivimab/etesevimab.

Discussion

Our findings provide a comprehensive analysis of the risk factors associated with persisting SARS-CoV-2 infection in patients with B-cell malignancies. They emphasize the importance of identifying and treating at-risk patients early, given the substantial morbidity associated with persistence.

A recent large-scale community surveillance study estimated that 0.1-0.5% of SARS-CoV-2 infections in the general population may become persistent, highlighting that persisting infections in immunocompromised patients could serve as reservoirs for viral evolution. However, the prevalence in high-risk patients was not assessed, leaving this issue unsolved [8]. Several retrospective observational studies have attempted to estimate the prevalence

Table 2
Multivariable logistic regression identifying predictors of persistent SARS-CoV-2 infection.

	Odds ratio	95% confidence interval	*P*-value
Age (years)	0.996	0.981-1.011	0.592
Male	0.881	0.355-2.189	0.785
Malignancy			
Chronic lymphocytic leukemia	0.601	0.275-1.312	0.201
Hodgkin lymphoma	0.216	0.032-1.442	0.114
Multiple myeloma	4.237	0.508-35.362	0.182
Non-Hodgkin lymphoma	Reference		
Time from HM to index episode (months)	1.008	1.002-1.013	0.004
Tixagevimab/cilgavimab use[a]	4.645	1.112-19.395	0.035
Anti-CD20 antibody therapy[b]	3.225	2.368-4.391	<0.001
Hospital admission at index episode	5.160	2.368-12.447	<0.001
Early antiviral treatment			
Molnupiravir	0.544	0.240-1.231	0.144
Nirmatrelvir/r	0.322	0.193-0.539	<0.001
Remdesivir	0.255	0.176-0.370	<0.001
None	Reference		
Sotrovimab as early treatment	0.324	0.153-0.686	0.003
Constant	0.225	0.095-0.533	0.001

[a] In the last 6 months or first 10 days of index episode. [b]In the previous 24 months

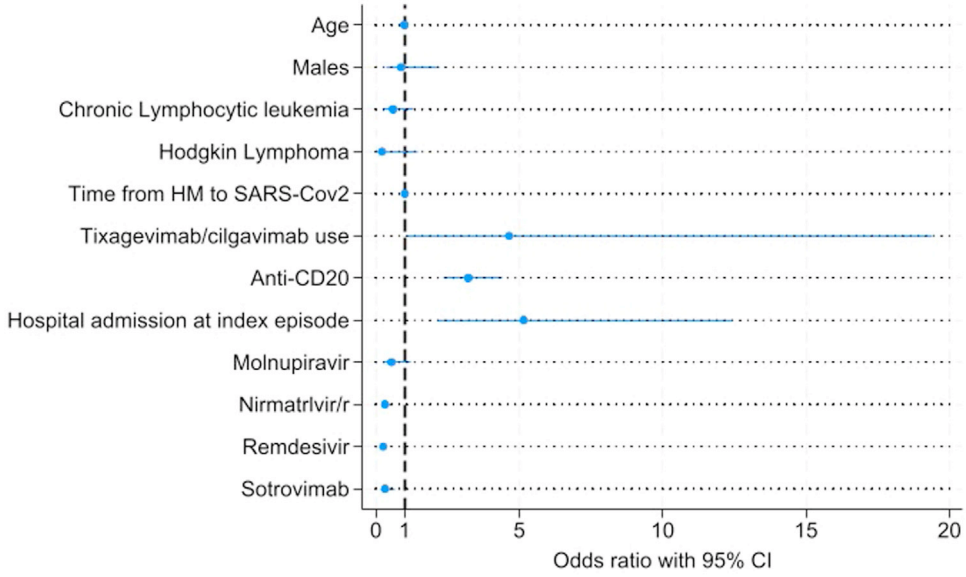

Figure 1. Coefficient plot of the multivariable logistic regression model identifying independent risk factors associated with persisting SARS-CoV-2 infection. CD, clusters of differentiation; CI, confidence interval.

of persisting COVID-19 in immunocompromised patients with B-cell malignancies. However, these studies have been limited by small sample sizes and a high degree of variability due to challenges in tracking all infections, including asymptomatic or mildly symptomatic cases, and differences in infection screening strategies [7,18,19]. Similarly, our study found substantial variability between centers, with the frequency of persisting SARS-CoV-2 infection in this high-risk population ranging from 16.8–84.2%. The overall frequency was 26.1%, consistent with existing literature and confirming a markedly higher risk of persisting SARS-CoV-2 infection in patients with B-cell malignancies. However, larger epidemiological studies are needed to more accurately define the prevalence in this vulnerable population.

Beyond assessing its frequency, several factors were identified as being associated with the development of persisting COVID-19. Multivariable analysis revealed that recent anti-CD20 treatment, time from HM diagnosis, need for hospitalization at initial diagnosis, and tixagevimab/cilgavimab administration were independently associated with an increased risk, while effective early therapy was protective.

Among the hematologic treatments administered, anti-CD20 therapies emerged as the strongest predictor of persistence, as widely suggested in previous literature [20,21], further supporting the association between B-cell depletion and impaired viral clearance. Conversely, BTKi were associated with a lower risk in bivariate analyses, likely reflecting their use as alternatives to anti-CD20. Bendamustine, modeled separately from anti-CD20, was not independently associated with persistence, differing from prior cohort studies in which it was commonly combined with anti-CD20, potentially confounding the outcome [19,21,22]. Although limited by the small numbers of exposed patients (33 and 67 for bendamustine and BTKi, respectively), these findings suggest that these agents may not significantly affect viral clearance and may help guide decisions on whether to temporarily discontinue treatment during acute SARS-CoV-2 infection.

Previous CAR-T therapy was significantly more frequent in the persisting group in bivariate analyses, whereas HSCT showed no significant difference. These findings appear to confirm previous studies indicating a higher risk of persisting infection in CAR-T recipients [23,24]. However, neither factor remained significant in the multivariable analysis, likely due to the limited number of cases.

Apart from hematologic factors, the severity of the acute SARS-CoV-2 infection played a crucial role in persistence. Patients

requiring hospitalization at the time of initial infection and those with radiological evidence of pneumonia had a significantly higher risk of developing persisting SARS-CoV-2 infection, supporting the hypothesis that severe acute disease predisposes to prolonged viral replication and delayed immune clearance [7,10]. In contrast, early antiviral treatment with nirmatrelvir/ritonavir and remdesivir was associated with a markedly reduced risk of persistence, reinforcing the importance of prompt therapeutic intervention, as also suggested by previous studies in immunocompromised patients [25]. The lack of protection with molnupiravir also aligns with randomized and real–world evidence [26]. Notably, early sotrovimab use was associated with a lower risk of persistence, supporting its potential utility in this setting. Nevertheless, administrations were concentrated in the first months of 2022, when Omicron BA.1 predominated, and declined thereafter as less-susceptible subvariants emerged. Since systematic genomic sequencing was not performed, variant-specific effectiveness could not be determined.

Regarding vaccination, no significant protective effect against persistence was observed, likely due to the high overall vaccination rate. Interestingly, although vaccination rates and doses were similar between groups, patients with persisting infection had a longer interval since their last vaccine dose. This finding suggests that waning immunity, rather than primary vaccine failure, may contribute not only to breakthrough infections, as previously demonstrated in other clinical settings [27], but also to persisting infection. The association between vaccination and persisting infection in this high-risk population remains limited and somewhat conflicting [28,29], highlighting the need for alternative prophylactic strategies to enhance protection in these patients. Interestingly, the use of tixagevimab/cilgavimab was unexpectedly found to be associated with the development of persisting COVID-19. This finding suggests a potential interaction between this therapy and the patient's immune response, which warrants further investigation in future studies.

From a clinical perspective, persisting SARS-CoV-2 infection was associated with significant morbidity, with a median time to virological clearance of 51 days and lower rates of clinical resolution. Although mortality was numerically higher in the persisting infection group, this difference did not reach statistical significance, likely due to the high overall frailty of the study population.

This study has several limitations. Its retrospective design introduced potential selection biases: differences in screening strategies and diagnostic approaches between centers may have influenced the observed variability in persistence rates. Moreover, the lack of genotypic testing prevented us from distinguishing between relapse and reinfection events during the 120-day follow-up. Consequently, we adopted the more general term 'recurrence' to describe these cases. Another limitation is the underrepresentation of newer B-cell–specific therapies, which are increasingly used in the management of B-cell malignancies and may play a significant role in susceptibility to persisting SARS-CoV-2 infection [30]. Future studies should aim to include these emerging treatments to provide a more comprehensive risk assessment.

To conclude, given the substantial morbidity associated with persistence, future research should focus on refining risk factors and evaluating the efficacy of novel immunomodulatory and antiviral interventions.

Declaration of competing interest

ZP Speaker for Gilead, Pfizer, AstraZeneca; MG Speaker for Gilead, Pfizer; PV Speaker for Gilead, Pfizer, MSD, AstraZeneca. All other authors report no conflicts of interest.

Funding

This work was supported by the European Union's Horizon 2020 Research and Innovation Program, grant agreement 101016167, within the ORCHESTRA project (EU H2020 ORCHESTRA).

Ethical approval

This retrospective observational study was conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments. Ethical approval was obtained from the coordinating center's ethics committee IRCCS - Azienda Ospedaliera-Universitaria di Bologna, and subsequently from all participating centers according to local regulations. Due to the retrospective nature of the study and the use of anonymized data, informed consent was waived as per local ethics requirements.

Author contributions

ZP, AT and MG conceived the study design. ZP, AT, AA, BC, CP, AD, PDM, LB, MC, AV, PON, and ORCHESTRA study group collected data. DG performed statistical analysis. ZP, AT, and DG interpreted results. ZP drafted the manuscript. AV, PON, MB, EN, MK, PLZ, FB, PV, ZPB, ET, and MG critically revised the manuscript. All authors approved the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108053.

References

[1] Pinato DJ, Aguilar-Company J, Ferrante D, Hanbury G, Bower M, Salazar R, et al. Outcomes of the SARS-CoV-2 omicron (B.1.1.529) variant outbreak among vaccinated and unvaccinated patients with cancer in Europe: results from the retrospective, multicentre, OnCovid registry study. *Lancet Oncol* 2022;**23**:865–75. doi:10.1016/S1470-2045(22)00273-X.

[2] Sun J, Zheng Q, Madhira V, Olex AL, Anzalone AJ, Vinson A, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. *JAMA Intern Med* 2022;**182**:153–62. doi:10.1001/jamainternmed.2021.7024.

[3] Evans RA, Dube S, Lu Y, Yates M, Arnetorp S, Barnes E, et al. Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study. *Lancet Reg Health Eur* 2023;**35**:100747. doi:10.1016/j.lanepe.2023.100747.

[4] DeWolf S, Laracy JC, Perales MA, Kamboj M, van den Brink MRM, Vardhana S. SARS-CoV-2 in immunocompromised individuals. *Immunity* 2022;**55**:1779–98. doi:10.1016/j.immuni.2022.09.006.

[5] Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, et al. SARS-CoV-2 evolution during treatment of chronic infection. *Nature* 2021;**592**:277–82. doi:10.1038/s41586-021-03291-y.

[6] Zhou B, She J, Wang Y, Ma X. Duration of viral shedding of discharged patients with severe COVID-19. *Clin Infect Dis* 2020;**71**:2240–2. doi:10.1093/cid/ciaa451.

[7] Lee CY, Shah MK, Hoyos D, Solovyov A, Douglas M, Taur Y, et al. Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies. *Cancer Discov* 2022;**12**:62–73. doi:10.1158/2159-8290.CD-21-1033.

[8] Ghafari M, Hall M, Golubchik T, Ayoubkhani D, House T, MacIntyre-Cockett G, et al. Prevalence of persistent SARS-CoV-2 in a large community surveillance study. *Nature* 2024;**626**:1094–101. doi:10.1038/s41586-024-07029-4.

[9] Hettle D, Hutchings S, Muir P, Moran E. COVID-19 Genomics UK (COG-UK) consortium. Persistent SARS-CoV-2 infection in immunocompromised patients facilitates rapid viral evolution: retrospective cohort study and literature review. *Clin Infect Pract* 2022;**16**:100210. doi:10.1016/j.clinpr.2022.100210.

[10] Götz V, Mathé P, Agarwal P, Hornuss D, Pfau S, Panning M, et al. Clinical phenotype and outcome of persistent SARS-CoV-2 replication in immunocompromised hosts: a retrospective observational study in the Omicron era. *Infection* 2024;**52**:923–33. doi:10.1007/s15010-023-02138-0.

[11] Dioverti V, Salto-Alejandre S, Haidar G. Immunocompromised patients with protracted COVID-19: a review of "long persisters. *Curr Transplant Rep* 2022;**9**:209–18. doi:10.1007/s40472-022-00385-y.

[12] Belkin A, Leibowitz A, Shargian L, Yahav D. The unique presentation of SARS-CoV-2 infection in patients with B-cell depletion: definition of 'persistent inflammatory sero-negative COVID. *Clin Microbiol Infect* 2023;**29**:1–3. doi:10.1016/j.cmi.2022.10.007.

[13] World Health Organization (WHO) clinical case definition working group on post COVID-19 condition *A clinical case definition of post COVID-19 condition by a Delphi consensus*. Geneva: World Health Organization; 2021.
[14] Baldi F, Dentone C, Mikulska M, Fenoglio D, Mirabella M, Magnè F, et al. Case report: Sotrovimab, remdesivir and nirmatrelvir/ritonavir combination as salvage treatment option in two immunocompromised patients hospitalized for COVID-19. *Front Med (Lausanne)* 2022;**9**:1062450. doi:10.3389/fmed.2022.1062450.
[15] Ford ES, Simmons W, Karmarkar EN, Yoke LH, Braimah AB, Orozco JJ, et al. Successful treatment of prolonged, severe COVID-19 lower respiratory tract disease in a B-cell ALL patient with an extended course of remdesivir and nirmatrelvir/ritonavir. *Clin Infect Dis* 2023;**76**:926–9. doi:10.1093/cid/ciac868.
[16] Pasquini Z, Toschi A, Casadei B, Pellegrini C, D'Abramo A, Vita S, et al. Dual combined antiviral treatment with remdesivir and nirmatrelvir/ritonavir in patients with impaired humoral immunity and persistent SARS-CoV-2 infection. *Hematol Oncol* 2023;**41**:904–11. doi:10.1002/hon.3206.
[17] World Health Organization *Clinical management of COVID-19: living guideline*. Geneva: World Health Organization; 2023.
[18] Lamure S, Dulery R, Delord M, Di Blasi R, Chauchet A, Hueso T, et al. Abstract S09-02: High incidence of persistent COVID-19 among patients with lymphoma treated with B-cell depleting immunotherapy. *Clin Cancer Res* 2021;**27** S09-S02. doi:10.1158/1557-3265.COVID-19-21-S09-02.
[19] Lee JA, Han M, Ahn S, Lee Y, Yeom JS, Choi JY, et al. Long-term outcomes of COVID-19 and risk factors for prolonged or persistent COVID-19 in lymphoma patients: a multicenter, retrospective cohort study. *J Korean Med Sci* 2024;**39**:e263. doi:10.3346/jkms.2024.39.e263.
[20] Gaitzsch E, Passerini V, Khatamzas E, Strobl CD, Muenchhoff M, Scherer C, et al. COVID-19 in patients receiving CD20-depleting immunochemotherapy for B-cell lymphoma. *Hemasphere* 2021;**5**:e603. doi:10.1097/HS9.0000000000000603.
[21] Maruyama S, Wada D, Kanayama S, Shimazu H, Miyano Y, Inoue A, et al. The evaluation of risk factors for prolonged viral shedding during anti-SARS-CoV-2 monoclonal antibodies and long-term administration of antivirals in COVID-19 patients with B-cell lymphoma treated by anti-CD20 antibody. *BMC Infect Dis* 2024;**24**:715. doi:10.1186/s12879-024-09631-3.
[22] Franceschini E, Pellegrino M, Todisco V, Dolci G, Bettelli F, Meschiari M, et al. Persistent SARS-CoV-2 infection with multiple clinical relapses in two patients with follicular lymphoma treated with Bendamustine and obinutuzumab or rituximab. *Infection* 2023;**51**:1577–81. doi:10.1007/s15010-023-02039-2.
[23] Meir J, Abid MA, Abid MB. State of the CAR-T: risk of infections with chimeric antigen receptor T-cell therapy and determinants of SARS-CoV-2 vaccine responses. *Transplant Cell Ther* 2021;**27**:973–87. doi:10.1016/j.jtct.2021.09.016.
[24] Infante MS, Nemirovsky D, Devlin S, DeWolf S, Tamari R, Dahi PB, et al. Outcomes and management of the SARS-CoV2 Omicron variant in recipients of hematopoietic cell transplantation and chimeric antigen receptor T cell therapy. *Transplant Cell Ther* 2024;**30**:116.e1–116.e12. doi:10.1016/j.jtct.2023.09.027.
[25] Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. Nirmatrelvir-ritonavir and COVID-19 mortality and hospitalization among patients with vulnerability to COVID-19 complications. *JAMA Netw Open* 2023;**6**:e2336678. doi:10.1001/jamanetworkopen.2023.36678.
[26] Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet* 2023;**401**:281–93. doi:10.1016/S0140-6736(22)02597-1.
[27] Kornek B, Leutmezer F, Rommer PS, Koblischke M, Schneider L, Haslacher H, et al. B cell depletion and SARS-CoV-2 vaccine responses in neuroimmunologic patients. *Ann Neurol* 2022;**91**:342–52. doi:10.1002/ana.26309.
[28] Ye L, Yang Y, Zhang X, Wang L, Zhu L, Li X, et al. Inactivated vaccine dosage and serum IgG levels correlate with persistent COVID-19 infections in hematologic malignancy patients during the Omicron surge in China. *BMC Infect Dis* 2024;**24**:1141. doi:10.1186/s12879-024-10063-2.
[29] Kanai O, Fujita K, Hata H, Odagaki T, Mio T. Duration of viable SARS-CoV-2 shedding in immunocompromised COVID-19 patients during the widespread vaccination era. *Open Forum Infect Dis* 2023;**10** ofad500.2244. doi:10.1093/ofid/ofad500.2244.
[30] Kyvsgaard ER, Riley C, Clausen MR, Harsløf M, Heftdal LD, Niemann CU, et al. Low mortality from COVID-19 infection in patients with B-cell lymphoma after bispecific CD20xCD3 therapy. *Br J Haematol* 2024;**204**:356–60. doi:10.1111/bjh.19156.