Study code: PERsiCO

Evaluation of prevalence and risk factors of persistent SARS-CoV-2 infection in immunocompromised patients

Author (s):	Maddalena Giannella, Zeno Adrien Igor Pasquini, Alice Toschi, Pierluigi Viale

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PROTOCOL SIGNATURES PAGE

Protocol Code: PERsiCO

(Author) *Maddalena Giannella*	signature	11-Oct-2023 Date
(Author) *Zeno Adrien Igor Pasquini*	signature	date
(Author) *Alice Toschi*	signature	date
(Author) *Pierluigi Viale*	signature	date

INVESTIGATOR'S STATEMENT:

Protocol Code: PERsiCO

I declare that I have read the protocol and agree to conduct this clinical study in accordance with all the requirements of the protocol and in accordance with the Guidelines of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

Maddalena Giannella		11-Oct-2023
(Principal Investigator)	signature	date

CONTENT INDEX

1. Study-specific abbreviations and terms

Anti-CD20	Anti-cluster of differentiation 20
AOU	Azienda Ospedaliera-Universitaria
CAR-T	Chimeric antigen receptor T cell
COVID-19	Coronavirus disease 2019
CT	Cycle threshold
HCT	Hematopoietic Cell Transplant
ICU	Intensive care unit
IRCCS	Istituto di ricovero e cura a carattere scientifico
LRTI	Lower respiratory tract infection
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOT	Solid Organ Transplant
WHO	World Health Organization

2. Introduction

2.1 Background and rationale

Although the impact of COVID-19 has been significantly reduced thanks to the effectiveness of vaccination and antiviral treatments, the risk of breakthrough infection remains higher in the immunocompromised population [1].

Immunocompromised patients are at increased risk for SARS-CoV-2-associated morbidity and mortality due to immunologic deficits that limit normal immune response and viral clearance [2-3]. Furthermore, the type of immunosuppression and the treatments performed significantly impact the natural trajectory of the COVID-19 infection, as in the case of patients with impaired adaptive humoral immunity who are relatively protected from acute infectious toxicity but have a high risk of prolonged viral shedding, viral rebound, and chronic infection [2-3].

In this group of patients, also known as “long persisters”, we find especially haematological patients with B cell malignancies or undergoing B cell targeting therapies such as anti-CD20 and CAR-T cell therapy. These patients, in addition to the complications related to SARS-CoV-2 infection itself, represent a particularly interesting population as the lack of viral clearance can lead to delays in life-saving treatments.

Despite major advances in our understanding of COVID-19, there is still a lack of consensus on how to define the condition of persistent infection in immunocompromised patients, also called “protracted SARS-CoV-2 infection” or “persistent inflammatory sero-negative COVID” [4-5]. In particular, two recent studies have tried to distinguish this phenomenon from "long COVID-19" and "post-COVID-19 condition", which is defined by the WHO as a syndrome that occurs in individuals who have contracted COVID-19 in the previous 3 months and have at least 2 months of ongoing symptoms (such as fatigue, dyspnoea, and cognitive dysfunction), with no alternative diagnoses [6]. Both studies [4-5] suggest the use of diagnostic criteria that combine baseline host immunodeficiency, clinical signs and virological data, which we can summarize as follows:

- Host criterion: underlying immunosuppression such as HCT, CAR T-cell recipient, lymphoma or B-cell malignancy, SOT, Anti-CD20 therapy or other B/T cell targeted therapies, primary and acquired immunodeficiencies.
- Clinical criterion: persistent/relapsing symptoms (fever, dyspnea, hypoxemia) and/or persistent/relapsing changes on chest-X ray or CT scan after extensive negative infectious work up.
- Virological criterion: persistently positive SARS-CoV-2 PCR $\geq$ 21 days.

Although 21 days may not be a particularly long duration in this type of patient, in this study we will use this time reference to identify patients with persistent infection.

Current COVID-19 treatment guidelines recommend the use of a single agent within few days of symptoms for all the patients with mild disease but with risk factors for progression

to severe disease, including immunocompromised condition. Remdesivir remains the only approved antiviral to treat hospitalized patients with COVID-19 in case of progression to LRTI and, in any case, after 10 days from diagnosis patients are no longer eligible for any treatment. Moreover, specific indications for immunocompromised patients are limited to the use of long-acting monoclonal antibodies as SARS-CoV-2 pre-exposure prophylaxis for individuals who may have an inadequate immune response to COVID-19 vaccination. It should also be specified that there is currently insufficient evidence to guide clinical recommendations for other treatments in immunocompromised patients [7].

However, in clinical practice, it appears clear that such recommendations are not sufficient to guarantee the cure of SARS-CoV-2 infection in immunocompromised patients, in particular in the "long persisters" population. Currently in literature, only case reports or small case series have described the prevalence and the management of patients with persisting infection. These studies show a wide variability of therapeutic approaches ranging from the adoption of repeated or prolonged cycles of remdesivir [8-10] or nirmatrelvir/ritonavir [11], dual antiviral therapy [12-13] and combination therapy with antiviral and monoclonal antibodies [14-16]. These case reports show variable success rates and highlight the need for larger studies focused on immunocompromised patients, to identify the best therapeutic approach in this population.

With this premise, we would like to conduct an observational study on immunocompromised patients, and specifically on haematological patients with B cell malignancies diagnosed with SARS-CoV-2 infection, with the aims of assessing the prevalence of those with persisting COVID-19, associated risk factors and describe the different clinical managements and their related outcomes.

2.2 Importance of the study and its clinical relevance

This study is part of the EU H2020 project "Connecting European Cohorts to Increase Common and Effective Response to SARS-CoV-2 Pandemic: ORCHESTRA" (Grant Agreement n. 101016167), which addresses task 4.6 *"Prevalence, risk factors and therapeutic management of persisting COVID-19 in fragile patients"*.

We deem that the results of our study could help improve the management of immunocompromised patients at risk for developing persisting COVID-19, Indeed, by describing the burden, host, risk factors, therapeutic management and outcome of immunocompromised patients with persisting COVID-19, we may inform future interventional studies and current clinical practice regarding a currently unmet need with controversial evidence.

3. Objectives of the study

3.1 Primary objective

The primary objective of this study is to describe the prevalence of SARS-CoV-2 persisting infection and the related risk factors in immunocompromised patients with B cell malignancies or undergoing B cell targeting therapies.

3.2 Secondary objectives

The secondary objective of the study is to describe and compare between patients with and without persisting COVID-19 the clinical, virological and radiological outcomes and the different therapeutic approaches performed.

3.3 Endpoints

The first primary endpoint variable will be the prevalence of persisting SARS-CoV-2 infection among the immunocompromised patients defined as the persistence or the recurrence of symptoms and signs (fever, dyspnea, hypoxemia, changes on chest-X ray or CT scan) and positive SARS-CoV-2 PCR $\geq$ 21 days after the time 0 (day of the first test positive for SARS-CoV2 infection).

The endpoints for the secondary objectives are:

- Duration of treatment carried out to address the persistent COVID-19 condition and treatment-related adverse effects.
- Duration of viral shedding, defined as the number of days between the first positive test and first negative PCR test.
- Duration of symptoms, defined as the number of days between symptoms onset and the clinical cure.
- Prevalence of imaging alterations, defined as the presence of new ground-glass and/or crazy paving and/or interstitial infiltrates at chest CT scan during the persisting infection (starting from 21 days after the first positive test until viral clearance).
- Re-infection within 120 days, define as new positive test with or without symptoms after viral clearance has been achieved.
- All-cause 120-day mortality.

4. Investigational plan

4.1 Study type

Cross-sectional study ..... ☐

Retrospective Case-control study ..... ☐

Retrospective cohort study ..... ☐

Prospective cohort study..... ☐

Retrospective and prospective cohort study ..... ☒

Descriptive pilot/feasibility study ..... ☐

Qualitative study..... ☐

4.2 Mono or multicenter study

Monocentric..... ☐

National multicenter ..... ☐

International multicenter ..... ☒

4.2.1 Multicenter study coordination

Alma Mater Studiorum – University of Bologna (UNIBO), Department of Medical and Surgical Sciences is the promoter of this study. The clinical center affiliated to UNIBO, which is the Infectious Disease Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna (IRCCS AOU of Bologna) Policlinico di Sant'Orsola, will be the coordinator center. Other clinical centers will be invited to share their data under the terms and conditions described in this protocol.

4.3 Study design

Spontaneous international multicenter retrospective and prospective observational study.

The retrospective recruitment period will span from 1.01.2022 to the date of authorisation by hospital directorates following the Ethics Committees' approvals. This period has been established considering the prevalent diffusion of the omicron variant and its subvariants, which has led to significant changes in the clinical manifestations of COVID-19. The prospective recruitment will be carried out over the 12 months immediately following the retrospective period.

During the study period, screening for persisting SARS-CoV-2 infection and therapeutic management of all patients will be carried out by the attending physicians according to routine practice.

4.4 Study population

All immunocompromised adults (≥18 years) with a new SARS-CoV-2 infection assessed during the study period, hospitalized or followed as outpatients in the Haematological Units of the participating centers, will be screened for inclusion.

4.4.1 Inclusion Criteria

- Diagnosis of B cell malignancies or previous treatment with B cell targeting therapies.

- Diagnosis of proven SARS-CoV-2 infection confirmed by a PCR test (only the first infection during the study period will be considered, re-infection will be counted as a secondary endpoint).

- Provision of signed and dated informed consent.

4.4.2 Exclusion Criteria

- None

4.4.3 Population size of the study and statistical power

According to the records of the Haematology Unit of IRCCS AOU of Bologna, from January 2022 to December 2022, 250 patients with underlying B cell malignancies have been diagnosed with SARS-CoV2 infection and we estimate that approximately 30% had viral shedding longer than 21 days. Thus, we deem that at the end of the study period, approximately 500 patients will be enrolled from IRCCS AOU of Bologna of which about 150 with prolonged infection. Considering the epidemiology of the other participating centers, we expect to reach an overall cohort of about 1000 immunocompromised patients with SARS-CoV-2 infection, with approximately 300 prolonged infections.

Power analysis carried out using Stata v.17.0 showed that a sample size of 1,000 allows to obtain power=80% and alpha=0.05 for a log-rank test comparing 120-days mortality, with a 300/700 allocation ratio, when the difference in mortality rates is at least 4% and mortality rate in the non-persistent COVID is as low as 3%, or when the difference in mortality rates is at least 5% and mortality rate in the non-persistent COVID is at least 4%.

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Estimated sample sizes for two-sample comparison of survivor functions
Log-rank test, Freedman method
H0: HR = 1  versus  Ha: HR != 1
```

alpha	power	N	N1	N2	nratio	E	delta	hratio	s1	s2	Pr_E
.05	.8	**897**	**627**	**270**	.43	59	2.054	2.054	.95	.9	.06503
.05	.8	**1,343**	**939**	**404**	.43	84	1.839	1.839	.95	.91	.06203
.05	.8	**2,282**	**1,596**	**686**	.43	135	1.626	1.626	.95	.92	.05902
.05	.8	**4,900**	**3,426**	**1,474**	.43	275	1.415	1.415	.95	.93	.05601
.05	.8	**18662**	**13050**	**5,612**	.43	990	1.206	1.206	.95	.94	.05301
.05	.8	.	.	.	.43	.	1	1	.95	.95	.
.05	.8	**561**	**392**	**169**	.43	33	2.581	2.581	.96	.9	.05804
.05	.8	**768**	**537**	**231**	.43	43	2.31	2.31	.96	.91	.05503
.05	.8	**1,140**	**797**	**343**	.43	60	2.043	2.043	.96	.92	.05203

.05	.8	**1,918**	**1,341**	**577**	.43	94	1.778	1.778	.96	.93	.04902
.05	.8	**4,070**	**2,846**	**1,224**	.43	188	1.516	1.516	.96	.94	.04601
.05	.8	**15304**	**10702**	**4,602**	.43	659	1.257	1.257	.96	.95	.04301
.05	.8	**367**	**256**	**111**	.43	19	3.459	3.459	.97	.9	.05105
.05	.8	**471**	**329**	**142**	.43	23	3.096	3.096	.97	.91	.04804
.05	.8	**638**	**446**	**192**	.43	29	2.737	2.737	.97	.92	.04503
.05	.8	**933**	**652**	**281**	.43	40	2.383	2.383	.97	.93	.04203
.05	.8	**1,545**	**1,080**	**465**	.43	61	2.031	2.031	.97	.94	.03902
.05	.8	**3,221**	**2,252**	**969**	.43	116	1.684	1.684	.97	.95	.03601

s1, s2 = survival rates in groups 1 and 2
N1, N2 = sample size required in groups 1 and 2.

As regards the analysis on prevalence of imaging alterations, due to the larger expected difference between the two groups, the population size of 1,000 is completely adequate.

4.5 Study duration

The study will be composed by:

- a prospective recruitment period of 1 year after Ethics Committes' approvals and directorates' permissions to conduct the study (during which retrospective data will also be collected);
- Follow-up period of 120-days from the diagnosis of SARS-CoV-2 infection;
- Data collection and analysis, that will last 6 months

For an overall duration of approximately 22 months

4.6 Funding

Is there any funding for the study?

No ..... ☐

Yes, with internal grants ..... ☐

Yes, by institutional third parties..... ☒

Yes, from private third parties ..... ☐

4.7 Data management

Pseudonymized data will be collected using a pre-established electronic case report form (eCRF) developed using the REDCap capture tool hosted by CINECA, the Italian partner in charge of data management within the EU H2020 ORCHESTRA project. All centers will enter their data locally on the eCRF through internet connection. The principal investigator and/or her/his delegate will have access to all data in order to check for data integrity and advancement of data collection. Data sources will be clinical charts and hospital electronic records.

During all the study period, the principal investigator will inform investigators about the status of patient enrolment, follow-up, and data collection by newsletter periodically.

At the end of data collection, the principal investigator will be responsible for reviewing all data for integrity and accuracy. Queries will be generated and when necessary sent to

the local investigators for reviewing incomplete or inaccurate data. The database will be locked after fulfilment of all the queries.

4.8 Statistical Analysis Plan

Patients' characteristics will be summarized using absolute frequencies and percentages (categorical variables) and mean±standard deviation or median and interquartile range (scale variables, according to their distribution).

The prevalence of persisting SARS-CoV-2 infection among the immunocompromised patients will be obtained as the ratio of the number of patients with evidence of persisting SARS-CoV-2 infection on the total number of enrolled patients.

As for the analysis of risk factors for persisting COVID, comparisons between COVID-persistent and non-persistent patients will be carried out by means of survival analyses for all outcomes expressed as durations (time-to-event analyses). These outcomes will be compared by estimating Kaplan-Meier curves, calculating log-rank tests and multiple Cox regressions in which COVID persistance will be the main risk factor and including the confounders and effect modifiers listed below.

- Age
- Sex
- Comorbidities (Charlson Comorbidity Index)
- Underlying hematologic disease state
- Chemotherapy treatments performed
- Duration of Hospital stay
- Admissions to intensive care
- Days with central venous catheter
- Bacterial and fungal superinfections
- Vaccination status
- Previous SARS-CoV-2 infections
- Serological status (anti-SARS-CoV-2 antibodies)

Re-infection and imaging alterations rates will be calculated as the ratio of the number of events to the overall number of patients, and the comparison between persisters and non-persisters will be carried out by calculating the corresponding risk ratios. A multiple logistic regression model will assess the relationship between exposure and re-infection (image alteration) net of the potential confounders.

For secondary aims, the secondary endpoints will be described just for the patients with peristing COVID, categorical variables will be reported as number and relative

frequencies, continuous variables will be reported as mean±SD or median and IQR according with their distribution.

5. Administrative procedures and declarations

5.1 Informed consent and consent to the processing of personal data

The study protocol, any protocol amendment, informed consent, consent to the processing of personal data and any other information for patients must be approved by the Ethics Committee.

To participate in the study, each patient must provide written informed consent as well as consent to the processing of their personal data. In case it will be not possible to acquire informed consent (*e.g.* deceased or untraceable patients), data will be collected anonymously, meaning that possible patient identifiers will be removed.

5.1.1 Methods of acquiring informed consent and consent to the processing of personal data

Informed consent will be obtained by local investigators in collaboration with the attending physicians. For the retrospective cohort, it will be obtained during the standard scheduled follow-up visits. However, for those cases where it will not be possible to acquire consent, anonymized data (thus lacking a key that indirectly identifies the patient) may be recorded in the CRF. For the prospective cohort, informed consent will be administered to the patients at the enrolment. Only patients who will provide informed consent will be enrolled.

5.2 Study – specific insurance

Considering the nature of the study, a specific insurance is considered unnecessary.

5.3 Amendments to the protocol and changes to the conduct of the study

If during the enrolment period, the principal and local investigators will agree that any deviation from the original protocol is needed to reach the predefined sample size and/or to avoid bias in the assessment of outcomes, the protocol will be revised and an amendment will be submitted to Ethic Committees.

5.4 Conclusion of the study

After the lock of database, preliminary results will be shared with all the investigators in order to plan publication and other dissemination activities. These results will be used to communicate to local Ethic Committees the conclusion of the study.

5.5 Publication policy

Preliminary results will be revised by all the investigators in order to refine statical analysis, and to plan publication and other dissemination activities (presentation of results at International Congresses of Infectious Diseases and Transplant Societies).

For authorship, Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) will be followed. The ICMJE recommends that authorship be based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be 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.

According to the rules of good scientific practice, the principal investigator can claim the position of last author if he/she is not already first author. In the case of several research project leaders, they should agree on the last authorship among themselves at an early stage; in this context, shared first and last authorships should also be considered. As a rule, the "corresponding author" should be the research project leader with primary responsibility. The middle group of co-authors will be included according to contribution to the manuscript as the ICMJE recommendations.

5.6 Documentation archive

The principal investigator is responsible for the archiviation and conservation of the essential documents of the study, before, during and after the study conduction, according to the Italian law and good clinical practice.

Patient data will be gathered pseudo-anonymously, included subjects will be identified by a number/code. Principal and local investigators will keep the original data of the patient and his personal informed consent in a safe place.

5.7 Inspections/checks

If a regulatory authority will request an inspection, the principal investigator will soon inform the Ethic Committee.

5.8 Contact persons

Contacts (telephone numbers and emails) of the involved physicians are reported in the Investigator Folder for the local center.

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