# Screening for SARS-COV-2 Using RT-qPCR in Patients with Hematologic Neoplasms Receiving Chemotherapy

**Ignacio Martín Santarelli[1,2], Mariela Sierra[2,3], Sofía Isabel Fernández[1,2]**
[1]Departamento de Medicina, Universidad de Buenos Aires, Hospital de Clínicas "José de San Martín", Buenos Aires, Argentina;
[2]Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina;
[3]División de Infectología, Universidad de Buenos Aires, Hospital de Clínicas "José de San Martín", Buenos Aires, Argentina

Received October 12, 2022; Accepted January 13, 2023.

**Key words:** Hematologic neoplasms – Chemotherapy – COVID-19 testing – Asymptomatic disease

**Abstract:** It has been recommended that patients with leukaemias and lymphomas undergo universal screening for SARS-COV-2 using RT-qPCR before each treatment on the grounds of their high risk of experiencing severe forms of COVID-19. This raises a conflict with different recommendations which prioritise testing symptomatic patients. We found that among 56 RT-qPCR obtained in asymptomatic patients with hematologic neoplasms before chemotherapy administration, 2 (3.5%) were positive. A negative result did not exclude SARS-COV-2 infection in 1 patient (1.8%). It is unclear what the benefit of screening for SARS-COV-2 using RT-qPCR in patients with hematologic neoplasms who receive chemotherapy is.

**Mailing Address:** Ignacio Martín Santarelli, MD., Departamento de Medicina, Hospital de Clínicas "José de San Martín", Av. Córdoba 2351, Piso 11, C1120, Ciudad de Buenos Aires, Argentina; Phone: +549 11 5764 0610; e-mail: isantarelli@fmed.uba.ar

https://doi.org/10.14712/23362936.2023.3

## Introduction

The unprecedented sanitary, economic, and social consequences caused by the novel coronavirus SARS-COV-2 and its disease (COVID-19) are widely known, including over 500,000,000 confirmed infections and more than 6,000,000 deaths since the first case was notified in December 2019 (World Health Organization).

A retrospective study carried out in the United Kingdom with 1,044 patients with cancer who contracted COVID-19 determined that the subgroup of patients with hematologic malignancies (leukaemias, lymphomas and myelomas) had a 1.5-fold increased risk of experiencing severe disease, compared with those with solid tumours. Moreover, the former had a greater lethality (OR [odds ratio] = 2.25), and recent chemotherapy was independently associated with a greater mortality (OR = 2.09) (Lee et al., 2020).

On these grounds, different worldwide scientific societies have recommended universal screening for SARS-COV-2 using reverse-transcriptase polymerase chain reaction (RT-PCR) in nasal swabs obtained from asymptomatic patients with leukaemias who are to receive chemotherapy, before each treatment, and screening according to resource availability and the epidemiologic status in the case of Hodgkin lymphomas, with special concern for the lung injury bleomycin may cause (American Society of Hematology, European Hematology Association). Nevertheless, testing in asymptomatic populations, except for a few exceptions, conflicts with the recommendations issued by the World Health Organization, based on the lack of evidence of health impact and cost-effectiveness, and the prioritisation which should be given to symptomatic patients (World Health Organization).

In addition, the decisions made upon a positive test, such as delaying or suspending a chemotherapy, may result in devastating consequences in life-threatening diseases, as in the case of acute leukaemias.

It should not be forgotten that the sole detection of SARS-COV-2 genome in a RT-PCR test does not differentiate between an active infection and the excretion of non-infective viral particles. A determination which can be retrieved in a qualitative RT-PCR (RT-qPCR) is the cycle threshold (Ct), understood as the number of PCR cycles needed to amplify the viral DNA sequences up to a detectable level.

This value maintains an inverse relation with the viral load in the analysed sample. Even though it may be of use in certain selected cases, it has not been formally validated as a prognostic marker (Infectious Disease Society of America).

We aimed to determine the prevalence of asymptomatic detection of SARS-COV-2 genome in patients with hematologic neoplasms admitted to our hospital to receive chemotherapy. We also analysed the impact the positive results had in the clinical course of the infected patients.

## Methods

*Study setting and population*

We designed a retrospective, observational and descriptive study. We included the results of RT-qPCR in nasal swabs from patients older than 18 years of both genders, with diagnosis of leukaemias, lymphomas and myelomas, in any treatment phase, who were admitted to our hospital, a tertiary centre in Buenos Aires, Argentina, to receive chemotherapy from the first confirmed case of COVID-19 in Argentina, March 3rd, 2020, to February 28th, 2022.

We included patients with no symptoms compatible with COVID-19, that is, cough, fever (not even if ascribed to the hematologic disease), dyspnoea, headache, nausea, vomiting, myalgia, anosmia, or disgeusia, and without any unprotected exposure to confirmed COVID-19 patients, within the 7 days prior to admission. Also, the test had to be performed out of any clinical or radiological suspicion. As for patients with prior diagnosis of COVID-19, we only included those with a negative test between the disease and the admission.

The identity of the patients included was preserved. This study was approved by our Hospital's Ethics Committee (Comité de Ética del Hospital de Clínicas "José de San Martín" – IRB approval number: 112821). The procedures followed were in accordance with the Helsinki Declaration of 1975 (revised in 2013) of the World Medical Association.

*Data sources*

Data were retrospectively collected from medical charts. We registered clinical and epidemiologic information, and, for those patients with positive results, we also registered the Ct value in the respiratory sample. Our laboratory uses the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel 500 rxn (Integrated DNA Technologies, IDT® – Iowa, USA), based on N1 and N2 probes for detecting SARS-CoV-2, and the human RNaseP (RP) as an RNA extraction quality control. We obtained a mean value combining both results.

*Data analysis*

We determined the rate of SARS-COV-2 positivity among the asymptomatic patients. 95% confidence intervals (95% CI) were also calculated using the 2-sided Clopper-Pearson (exact) method. Statistical analysis was conducted using Stata® 13.1 (StataCorp).

We also analysed the clinical course of the SARS-COV-2 infection in the positive patients, and established what decision was made with regard to the chemotherapy treatment on each individual basis.

## Results

*Demographic and clinical characteristics*

56 RT-qPCR tests for SARS-COV-2 were eligible. The most remarkable characteristics of the patients involved are presented in Table 1.

**Table 1 – Characteristics of the origin of the respiratory samples used for SARS-COV-2 screening**

| | | N (%) |
|---|---|---|
| **Gender** | males | 26 (46.4) |
| | females | 30 (53.6) |
| | total | 56 (100) |
| **Age** | minimum | 19 |
| | maximum | 82 |
| | average | 47 |
| **Hematologic neoplasm** | lymphoma | 33 (58.9) |
| | acute lymphoblastic leukaemia | 13 (23.2) |
| | acute myeloid leukaemia | 8 (14.3) |
| | myeloma | 2 (3.6) |

N – number

*Primary outcome*

Among the total of RT-qPCR tests (n=56), 2 (3.5%; 95% CI = 0.3–12.8%) resulted positive for SARS-COV-2 genome. They belonged to adult males with a diagnosis of lymphoma who denied any related symptoms and had no evidence of clinical or radiological evidence of pneumonia. One of the Ct values was 30 cycles. We were not able to retrieve the other one. Since their clinical status was favourable, we decided to withhold the chemotherapy for 7 days. After this period of time, they received their treatments with no immediate or ulterior complications.

One 49-year-old female (1.8%; 95% CI = 0.004–9.5%) with diagnosis of lymphoblastic T-cell lymphoma had been admitted to receive consolidation treatment. On that day, 48 hours after a negative RT-qPCR test was obtained, she developed fever and odynophagia. The test was repeated and, this time, the result was positive, with a Ct = 26 cycles. She had no signs of pneumonia. The patient was discharged 3 days later fully recovered and returned for chemotherapy on the 10$^{th}$ day after symptom onset with no complications.

## Discussion

Patients with hematologic neoplasms have a higher risk of experiencing severe forms of respiratory infections, including COVID-19, than the general population, for several reasons related to the nature of their diseases and their treatments. Among them, these are the most relevant: 1) lymphopenia and neutropenia, 2) hypogammaglobulinemia, and 3) corticosteroid treatment (Assi et al., 2020). The American Society of Hematology reported a 28% mortality rate in a registry of 250 patients with hematologic neoplasms who contracted COVID-19 (Wood et al., 2020). In our country, that very same value was 20.8% (Basquiera et al., 2021).

The prevalence of asymptomatic infection by the novel coronavirus in patients with hematologic neoplasms in the population analysed (3.5%) was higher than reported by Shah et al. (2020) at a tertiary centre in New York: 0.64% among 621 PCR tests performed. In Wuhan, Yin et al. (2020) reported a 2.9% prevalence rate, but it was composed of patients with both lymphomas and solid tumours. We have not succeeded in finding local data to compare our results.

Several elements could influence these values: 1) the collection, storage and processing technique of the respiratory sample obtained by a nasal swab; 2) the homogeneity of the patient's selection criteria; 3) the exclusion of patients with fever which, it is widely known, may be a presenting symptom of acute leukaemia in up to 50–75% of cases (Gavillet et al., 2020). We bring this up because, if those patients whose disease presented with fever had been included, the prevalence would have most likely been even lower.

A standard RT-qPCR test performs a maximum of 40 cycles, after which the result is considered negative. *In vitro*, studies have shown that respiratory samples with Ct > 34 cycles do not possess the capability to infect cell cultures (La Scola et al., 2020). Both Ct values described in our manuscript were relatively high, which correspond to a low viral load.

The decision to withhold chemotherapy for 7 days was an extension of our local sanitary protocols for high-risk exposure and confirmed COVID-19 in immunocompetent patients, given the lack of compelling evidence for this particular population. Needless to say, we cannot tell what the clinical course would have been should we had administered the treatments at the time COVID-19 was diagnosed. On the other hand, the negative test of the female patient mentioned was followed by COVID-19 only 48 hours later, which is why we believe it was of no use, in terms of the purpose for which it was performed.

None of the three SARS-COV-2 positive patients received any specific treatment, as it was not indicated per our hospital's protocols. Each case was assessed on an individual basis, given the lack of universal guidelines. The Ct in the respiratory samples, albeit used with care since it has not been universally validated – as already stated – combined with a chest image, may guide clinical and therapeutic decisions such as whether to proceed with chemotherapy or not.

It is worth investigating whether remdesivir could lower the risk of disease progression in asymptomatic patients with haematological neoplasms. Although this was confirmed in general for outpatients, the cancer population was underrepresented (Gottlieb et al., 2022) and further specific studies are necessary.

These ideas should be highlighted: 1) the prevalence of asymptomatic SARS-COV-2 infection in patients with hematologic neoplasms is relatively low (studies report an even lower rate than our series, which was 3.5%) and its clinical implication is uncertain; 2) the economic cost of universal screening should be contextualised in a worldwide scenario of limited resources; 3) the interpretation of a positive result may be misleading and could derive in treatment delays with

devastating consequences in patients with, for example, an acute leukaemia; 4) a negative test only documents absence of viral excretion through the nasopharynx at the time of the testing. This being said, other screening methods could be considered.

To the best of our knowledge, there is no firm evidence that screening for SARS-COV-2 using RT-qPCR is better, in terms of cost-effectiveness, than the clinical and radiological (Meti et al., 2021). Each institution could consider confronting their own prevalence series with the economic cost of each RT-qPCR test performed.

## References

American Society of Hematology (2022) COVID-19 resources. Accessed June 1, 2022. Available at: https://www.hematology.org/covid-19

Assi, T., Samra, B., Dercle, L., Rassy, E., Kattan, J., Ghosn, M., Houot, R., Ammari, S. (2020) Screening strategies for COVID-19 in patients with hematologic malignancies. *Front. Oncol*. **10**, 1267.

Basquiera, A. L., García, M. J., Martinez Rolón, J., Olmedo, J., Laviano, J., Burgos, R., Caeiro, G., Remaggi, G., Raña, P., Paoletti, M., González, C. M., Fernández, I., Pavlovsky, A., Perusini, M. A., Rodriguez, A., Guanchiale, L., Carvani, A., Mandrile, L., Figueroa, F., Vicente Reparaz, A., Fragapane Mathus, P. N., Garate, G., Fauque, M. E., Kantor, G., Cruset, S., Gonzalez Lorch, J. S., Szelagowski, M., Giarini, M. P., Oliveira, N., García, M. C., Ventriglia, M. V., Pereyra, P. H., Gutierrez, D. R., Kusminsky, G., Troccoli, J., Freitas, M. J., Cranco, S., Del V Sanchez, N., Rey, J., Funes, M. E., Jarchum, S., Freue, J., Miroli, A., Guerrero, O., López Ares, L., Campestri, R., Bove, V., Salinas, G. N., Cabrejo, M., Milone, J. H., Zabaljauregui, S., Gotta, D., Dupont, J. C., Stemmelin, G. (2021) Clinical characteristics and evolution of hematological patients and COVID-19 in Argentina: A report from the Argentine Society of Hematology. *Medicina* **81(4)**, 536–545.

European Hematology Association (2022) COVID-19 and Hematology Information Center. Expert opinion for specific hematologic malignancies. Accessed June 6, 2022. Available at: https://ehaweb.org/covid-19/covid-19-recommendations/recommendations-for-specific-hematologic-malignancies/

Gavillet, M., Carr Klappert, J., Spertini, O., Blum, S. (2020) Acute leukemia in the time of COVID-19. *Leuk. Res*. **92**, 106353.

Gottlieb, R. L., Vaca, C. E., Paredes, R., Mera, J., Webb, B. J., Perez, G., Oguchi, G., Ryan, P., Nielsen, B. U., Brown, M., Hidalgo, A., Sachdeva, Y., Mittal, S., Osiyemi, O., Skarbinski, J., Juneja, K., Hyland, R. H., Osinusi, A., Chen, S., Camus, G., Abdelghany, M., Davies, S., Behenna-Renton, N., Duff, F., Marty, F. M., Katz, M. J., Ginde, A. A., Brown, S. M., Schiffer, J. T., Hill, J. A.; GS-US-540-9012 (PINETREE) Investigators (2022) Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N. Engl. J. Med*. **386(4)**, 305–315.

Infectious Disease Society of America (2022) IDSA and AMP joint statement on the use of SARS-CoV-2 PCR cycle threshold (Ct) values for clinical decision-making. Accessed June 6, 2022. Available at: https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-amp-statement.pdf

La Scola, B., Le Bideau, M., Andreani, J., Hoang, V. T., Grimaldier, C., Colson, P., Gautret, P., Raoult, D. (2020) Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur. J. Clin. Microbiol. Infect. Dis*. **39(6)**, 1059–1061.

Lee, L. Y. W., Cazier, J. B., Starkey, T., Briggs, S. E. W., Arnold, R., Bisht, V., Booth, S., Campton, N. A., Cheng, V. W. T., Collins, G., Curley, H. M., Earwaker, P., Fittall, M. W., Gennatas, S., Goel, A., Hartley, S., Hughes, D. J., Kerr, D., Lee, A. J. X., Lee, R. J., Lee, S. M., Mckenzie, H., Middleton, C. P., Murugaesu, N., Newsom-Davis, T., Olsson-Brown, A. C., Palles, C., Powles, T., Protheroe, E. A., Purshouse, K.,

Sharma-Oates, A., Sivakumar, S., Smith, A. J., Topping, O., Turnbull, C. D., Várnai, C., Briggs, A. D. M., Middleton, G., Kerr, R.; UK Coronavirus Cancer Monitoring Project Team (2020) COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: A prospective cohort study. *Lancet Oncol*. **21(10)**, 1309–1316.

Meti, N., Tahmasebi, H., Leahey, A., Boudreau, A., Thawer, A., Stewart, J., Reason, P., Albright, K., Leis, J. A., Katz, K., Cheung, M. C., Singh, S. (2021) SARS-CoV-2 testing for asymptomatic patients with cancer prior and during treatment: A single centre experience. *Curr. Oncol*. **28(1)**, 278–282.

Shah, M. A., Mayer, S., Emlen, F., Sholle, E., Christos, P., Cushing, M., Hidalgo, M. (2020) Clinical screening for COVID-19 in asymptomatic patients with cancer. *JAMA Netw. Open* **3(9)**, e2023121.

Wood, W. A., Neuberg, D. S., Thompson, J. C., Tallman, M. S., Sekeres, M. A., Sehn, L. H., Anderson, K. C., Goldberg, A. D., Pennell, N. A., Niemeyer, C. M., Tucker, E., Hewitt, K., Plovnick, R. M., Hicks, L. K. (2020) Outcomes of patients with hematologic malignancies and COVID-19: A report from the ASH Research Collaborative Data Hub. *Blood Adv.* **4(23)**, 5966–5975.

World Health Organization (2022) Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. Interim guidance 25 June 2021. Accessed June 6, 2022. Available at: https://apps.who.int/iris/bitstream/handle/10665/342002/WHO-2019-nCoV-lab-testing-2021.1-eng.pdf?sequence=1&isAllowed=y

World Health Organization (2022) WHO Coronavirus (COVID-19) Dashboard. Accessed June 6, 2022. Available at: https://covid19.who.int/

Yin, P., Zeng, R., Duan, Y. R., Zhang, Y., Kuang, X. N., Zhang, H. F., Wei, S. Z. (2020) An analysis of cancer patients with asymptomatic infection of SARS-CoV-2 in a cancer center in Wuhan, China. *Ann. Oncol.* **31(10)**, 1420–1422.