Descriptive analysis of cycle threshold in patients with hematologic malignancies infected with SARS-CoV-2

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Since the beginning of the SARS-CoV-2 pandemic, there has been much interest in developing a laboratory test which could predict the course and prognosis of the disease (CoViD-19). When a sample of the respiratory tract, for example one obtained through a nasal swab, is analyzed using a polymerase chain reaction (PCR) test, it is possible to determine the SARS-CoV-2 viral load with an indirect determination called cycle threshold (Ct). The higher the Ct, the lower the viral load, and vice versa. However, Ct has not yet been validated in the medical practice to make clinical decisions. We analyzed the Ct values of 15 patients with past hematologic malignancies (lymphomas and leukemias) who contracted CoViD-19 in order to establish whether those with lowest Ct values, that is, highest viral loads, had the most severe forms of CoViD-19.

KEY POINTS:

Current knowledge

Patients with hematologic malignancies have been proven to develop more serious forms of CoViD-19 than the general population. Cycle threshold is a numeric variable which can be obtained from a quantitative RT-PCR test for SARS-CoV-2. It holds an inverse correlation with the viral load in a fluid sample including nasopharyngeal swabs. Its reliability as a prognostic and infectivity indicator is controversial.

Contribution to knowledge

Cycle threshold determined in nasopharyngeal swabs from 15 patients with hematologic malignancies infected with SARS-CoV-2 was found to be lower in those who died and those who developed pneumonia. The viral shedding ranged between 22 and 158 days, with a mean of 79.3 days.

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ABSTRACT

Introduction: SARS-CoV-2 has caused over 200 million documented infections, more than 4 million deaths, and unprecedented consequences worldwide. The cycle threshold (Ct), the number of amplification cycles required to obtain a product detectable through fluorescence during a quantitative RT-PCR test, is an indirect measurement of viral load. Patients with hematologic malignancies have an increased risk of death by the SARS-CoV-2. **Cases presentation**: We conducted a retrospective, observational, descriptive analysis of the Ct obtained from patients with history of hematologic malignancies who tested positive for SARS-CoV-2 in our hospital, from March 3rd, 2020, to August 17th, 2021. We used the mean Ct at diagnosis. 15 adults, with previous diagnosis of lymphomas, acute leukemias and chronic lymphocytic leukemia, were included. 9 of the 15 patients (60 %) developed pneumonia, 6 of them required supplementary oxygen and 5 mechanical ventilation. 5 patients died between 7-86 days from symptom onset. Ct was lower among the group of patients who died (15.5 cycles; SD= 2.28, CI95%= 9.17-21.86) compared with those who survived (20.2 cycles; SD= 8.87, CI95%= 13.9-26.6). Ct was also lower in the pneumonia group (18.2 cycles; SD= 2.28, CI95%= 12.98-23.51) than in the no-pneumonia group (19.3 cycles; SD= 4.11; CI95%= 8.73-29.9). **Discussion**: Ct was lowest in severe forms of CoViD-19. Further studies with larger populations of patients with hematologic malignancies could establish the validity of Ct as a quantitative laboratory determination as a course-prediction and infectivity tool.

Keywords: polymerase chain reaction; hematologic neoplasms; coronavirus infections.

Análisis descriptivo del umbral de ciclado en pacientes con neoplasias hematológicas infectados con SARS-CoV-2

RESUMEN

Introducción: SARS-CoV-2 ha causado más de 200 millones de infecciones documentadas, más de 4 millones de muertes, y consecuencias sin precedentes globalmente. El umbral de ciclado (Ct), número de ciclos de amplificación requerido para obtener un producto detectable durante una prueba cuantitativa de RT-PCR, es una medida indirecta de la carga viral. Los pacientes con enfermedades oncohematológicas tienen mayor riesgo de muerte por SARS-CoV-2. **Presentación de casos**: Realizamos un estudio observacional, retrospectivo y descriptivo de los valores de Ct obtenidos de pacientes con enfermedades oncohematológicas que resultaron positivos para SARS-CoV-2 en nuestro hospital, desde el 3 de marzo de 2020, hasta el 17 de agosto de 2021. Empleamos el Ct promedio al diagnóstico. Fueron incluidos 15 adultos, con diagnóstico de linfomas, leucemias agudas y leucemia linfocítica crónica. 9 pacientes (60 %) desarrollaron neumonía, 6 requirieron oxígeno suplementario y 5 ventilación mecánica. 5 murieron a los 7-86 días desde el inicio de síntomas. Ct fue menor entre los pacientes que murieron (15.5 ciclos; DS= 2.28, IC95%= 9.17-21.86), comparado con los que sobrevivieron (20.2 ciclos; DS= 8.87, IC95%= 13.9-26.6). La misma tendencia se observó en el grupo de los que desarrollaron neumonía (18.2 ciclos; DS= 2.28, IC95%= 12.98-23.51), comparado con lo que no tuvieron neumonía (19.3 ciclos; DS= 4.11; IC95%= 8.73-29.9). **Discusión**: El valor de Ct fue más bajo en las formas más graves de CoViD-19. Estudios adicionales con poblaciones mayores de pacientes con enfermedades oncohematológicas podrían establecer la validez de Ct como determinación cuantitativa de laboratorio útil como predictora de evolución e infectividad.

Palabras claves: reacción en cadena de la polimerasa; neoplasias hematológicas; infecciones por coronavirus.

Análise descritiva do limiar de ciclismo em pacientes com neoplasias hematológicas infectadas com SARS-CoV-2

RESUMO

Introdução: O SARS-CoV-2 causou mais de 200 milhões de infecções documentadas, mais de 4 milhões de mortes e consequências sem precedentes em todo o mundo. O limiar de ciclagem (Ct), o número de ciclos de amplificação necessários para obter um produto detectável durante um teste quantitativo de RT-PCR, é uma medida indireta da carga viral. Pacientes com doenças oncohematológicas têm maior risco de morte por SARS-CoV-2. **Apresentação do caso**: Realizamos um estudo observacional, retrospectivo e descritivo dos valores de Ct obtidos de pacientes com doenças oncohematológicas positivos para SARS-CoV-2 em nosso hospital, de 3 de março de 2020 a 17 de agosto de 2021. Usamos o Ct médio no diagnóstico. Quinze adultos diagnosticados com linfomas, leucemia aguda e leucemia linfocítica crônica foram incluídos. 9 pacientes (60%) desenvolveram pneumonia, 6 necessitaram de oxigênio suplementar e 5 ventilação mecânica. 5 morreram dentro de 7-86 dias a partir do início dos sintomas. A Ct foi menor entre os pacientes que morreram (15,5 ciclos; DP= 2,28, IC95%= 9,17-21,86), comparados aos que sobreviveram (20,2 ciclos; DP= 8,87, IC95%= 13,9-26,6). A mesma tendência foi observada no grupo que desenvolveu pneumonia (18,2 ciclos; DP= 2,28; IC95%= 12,98-23,51), em relação aos que não tiveram pneumonia (19,3 ciclos; DP= 4,11; IC95%= 8,73-29,9). **Discussão**: O valor de Ct foi menor nas formas mais graves de CoViD-19. Estudos adicionais com populações maiores de pacientes com doenças oncohematológicas poderiam estabelecer a validade da Ct como uma determinação laboratorial quantitativa útil como preditor de evolução e infectividade.

Palavras-chave: reação em cadeia da polimerase; neoplasias hematológicas; infecções por coronavirus.

INTRODUCTION

The novel coronavirus SARS-CoV-2, since its first official report on December 31st, 2019, has caused over 200 million documented infections, more than 4 million deaths, and unprecedented consequences worldwide[1]. In December 2020, the American Society of Hematology released the results of the Research Collaborative CoViD-19 Registry[2], which included 250 patients with hematologic malignancies infected with the novel coronavirus. They reported a global mortality rate of 28 %. In our country, the Sociedad Argentina de Hematología (Argentinian Society of Hematology) published a similar registry with 419 patients from all over the country and established a global mortality of 20,8 %[3]. Either value is superior to the mortality rate in the general population according to the World Health Organization (2 %[4]). Since the emergence of the SARS-CoV-2, there has been an increasing interest in establishing reliable prognostic parameters to predict course severity and prognosis. Viral load has been studied for this purpose, based on previous experience on MERS-CoV[5] and SARS-CoV[6] pandemics in 2003 and 2012 respectively.

The detection of the viral genome using a real-time polymerase chain reaction (RT-PCR) is the standard molecular test for the etiologic diagnosis of SARS-CoV-2[7]. During a quantitative RT-PCR test (RT-qPCR), the number of amplification cycles required to obtain a product detectable through fluorescence is called cycle threshold (Ct)[8]. The Ct maintains an inverse correlation with the viral load in the analyzed sample: the lower the Ct, the higher the viral load, and vice versa. There has been a considerable effort in correlating the viral load in nasopharyngeal swab respiratory samples, with the mortality and prognosis of CoViD-19 in order to use it as a predictor of these outcomes. The evidence in this matter has been controversial and the routine use of Ct for clinical decision making is still not recommended [9-11]. Table 1 presents the factors that may affect the Ct value[11].

Table N° 1: Factors that may influence Ct value (11).

Patient factors	Specimen factors	Test factors
Presence of risk factors	Adequacy of specimen collection	Volume of sample tested
Severity of symptoms	Reproductibility of the specimen collection method	Gene target
Time from symptom onset	Source of specimen	PCR primer and probe design
Immune status	Transport medium used	Nucleic acid extraction efficiency
Age	Transport and storage conditions	Gene target amplification efficiency
		PCR instrument parameters and settings

Patients with cancer appear to have a greater risk for severe forms of CoViD-19 compared with healthy individuals. A multicentric study developed in New York analyzed the viral load of 100 patients with cancer and 2 914 patients without cancer. The SARS-CoV-2 viral load was classified as high (Ct < 25), intermediate (Ct 25-30) and low (>30). The researchers found that the presence of hematologic neoplasms was independently associated with a higher viral load on admission compared with patients without cancer, even after adjusting for possible confounders. High viral load was associated with higher mortality rates both in patients with and without cancer[9]. Moreover, Ct was lower among patients with hematologic neoplasms. To the best of our knowledge, no similar study has been performed in this particular population in Argentina.

We conducted a descriptive analysis of the Ct values of patients with history of hematologic malignancies who tested positive for SARS-CoV-2 in our hospital, in order to establish whether the lowest Ct values were found in the most severe forms of CoViD-19.

CASES PRESENTATION

We retrospectively recruited adult patients (over 18 years) with a history of hematologic malignancies (leukemias and lymphomas), who tested positive for SARS-CoV-2 using RT-qPCR in our hospital from March 3rd, 2020, to August 17th, 2021. We included patients who had been both admitted and treated in an out-patient basis.

We collected epidemiological, clinical, and laboratory data from past medical records. For each patient, we documented the Ct value in all nasopharyngeal swabs, that is, at diagnosis and during follow-up. Our laboratory uses the CDC designed FDA EUA 2019-nCoV CDC kit based on N1 and N2 probes for detecting SARS-CoV-2, and the human RNaseP (RP) as an RNA extraction quality control[12]. Therefore, for each nasopharyngeal swab analyzed, two results were reported, one for each probe (N1 and N2). We obtained a mean value combining both results. We used the Ct value at diagnosis. For the patients we were able to follow up with sequential testing, we calculated the time to SARS-CoV-2 clearance, understood as the time elapsed between the first detectable test and the undetectable result. The identity of the patients included was preserved. This study was approved by our Hospital's Ethics Committee.

From March 3rd, 2020, to August 17th, 2021, 15 patients with a history of hematologic malignancies who had a positive nasopharyngeal swab qRT-PCR test for SARS-CoV-2 were included. All of them had attended and been tested in our hospital and were either admitted or discharged.

6 individuals had a previous diagnosis of lymphoma, 5 had acute lymphoblastic leukemia, 3 were being treated for acute myeloid leukemia and only 1 for chronic lymphocytic leukemia. Our population consisted of 8 males and 7 females, whose age ranged between 19 and 70 years (mean age= 44,2). The most frequent comorbidities were diabetes mellitus (n=3), obesity (n=3), and smoking (n=3), followed by hypertension (n=2). 2 patients with lymphoma were HIV positive and had a $CD4^+$ count below 200 cells/mm^3. The most relevant characteristics of the population studied are presented in table 2.

Table N° 2: Main characteristics of our patients

Patient #	Gender	Age	Hematological neoplasm	Treatment phase	Other comorbilities	T test	Pneumonia	RF	MV	Death	TtD	Ct	T Clear
1	Female	34	ALL	Induction	Diabetes, overweight	1	Yes	Yes	Yes	No		11,8	78
2	Male	22	ALL	Refractory	Overweight	20	No	No	No	No		22,95	34
3	Male	49	Lymphoma	Untreated	HIV < 200 CD4+, smoking, overweight	0	Yes	No	Yes	Yes	50	19,9	
4	Male	61	Lymphoma	Maintainance	Hypertension, CKD	8	Yes	Yes	Yes	Yes	40	10,3	
5	Female	39	ALL	Induction	Obesity	5	No	No	No	No		15,85	39
6	Female	60	AML	Refractory	Diabetes, hypertension	3	Yes	Yes	No	Yes	58	20,4	
7	Male	42	AML	Induction	Obesity	2	Yes	Yes	Yes	Yes	7	17,1	
8	Male	20	ALL	Induction	-	1	No	No	No	No		11,5	45
9	Male	23	AML	Induction	Overweight	0	Yes	Yes	No	No		28	158
10	Male	19	ALL	Induction	-	6	No	No	No	No		37	22
11	Female	52	Lymphoma	Induction	HIV < 200 CD4+, diabetes, obesity	1	Yes	No	Yes	Yes	86	9,9	
12	Male	66	CML	Maintainance	Smoking, obsesity	4	Yes	Yes	No	No		18,75	98
13	Female	70	Lymphoma	Induction	Obesity	0	Yes	No	No	No		28,1	
14	Female	57	Lymphoma	Induction	-	0	No	No	No	No		8,85	98
15	Female	50	Lymphoma	Induction	Smoking	0	No	No	No	No		19,75	142

ALL: Acute lymphoblastic leukemia. AML: Acute myeloid leukemia. CML: Chronic myeloid leukemia. T Test: Time elapsed between symptom-onset and testing (days). RF: Respiratory failure. MV: Mechanical ventilation. TtD: Time to death since beggining of symptoms in days. Ct: Ct at diagnosis. T Clear: Time to SARS-CoV-2 clearance (days).

The most frequent symptom at presentation was fever (n=11), followed by dyspnea (n=5), cough (n=3), and anosmia/dysgeusia (n=3). 2 of our patients had asymptomatic CoViD-19 and were tested for epidemiologic reasons during admission for other non-infectious diseases.

The time elapsed between the symptom onset and the testing ranged between 1 and 20 days (mean= 3).

9 of the 15 patients (60 %) developed pneumonia and, among them, 6 required supplementary oxygen and 5 mechanical ventilation in the Intensive Care Unit. The number of days that elapsed from the symptom onset and the need for supplementary oxygen ranged between 3 and 59 (mean= 15.4). These patients needed supplementary oxygen for 2-27 days (mean= 15.7).

5 deaths were registered 7 to 86 days from symptom onset (mean= 48.2).

We were able to follow up 9 patients with subsequent tests after the first detectable result. The time to SARS-CoV-2 clearance ranged between 22 and 158 days, with a mean of 79.3 days (figure 1).

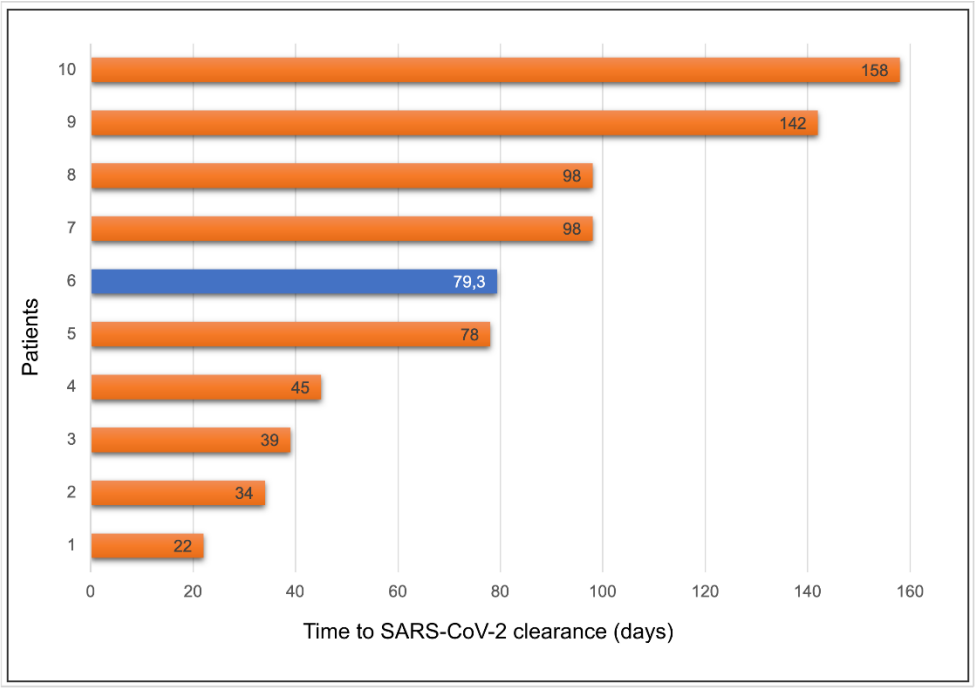

Figure N° 1: Time to SARS-COV-2 clearance in days. In blue, the mean value.

The mean Ct at diagnosis was 15.5 cycles among the patients who died (SD= 2.28; CI95%= 9.17-21.86), and 20.2 cycles in those who recovered from CoViD-19 (SD= 8.87; CI95%= 13.9-26.6). The variable analyzed was 18.2 cycles among the group of patients who developed pneumonia (SD=2.28; CI95%= 12.98-23.51), and 19.3 cycles in those who did not (SD= 4.11; CI95%= 8.73-29.9).

Discussion

To begin with, this observational, retrospective, descriptive, analysis of patients with hematologic malignancies infected with SARS-CoV-2, resulted in a relatively small population (n= 15). One hypothesis is that uninfected cancer patients limited their hospital visits and stayed safely home during lockdown. Some of the patients who had been diagnosed and treated for their hematologic malignancies could have attended other institutions for medical assistance for CoViD-19.

The frequency of presenting symptoms was similar to what other local studies reported in the general population[13], including the rate of asymptomatic positive testing (13.3 %).

Ct at diagnosis was lower in patients who developed pneumonia, compared with those who did not, and in those who died, compared with the survival group. Larger investigations in patients with hematologic malignancies could be developed in order to establish if there is a causal relation between the Ct and the outcomes analyzed. The small population of our study was a limitation for this objective.

Should this be confirmed, Ct could be used for at least two purposes: 1) Predict disease outcome, and 2) determine infectivity, to safely end isolation, instead of using a temporal criterion. Regarding this matter, it is worth mentioning that SARS-CoV-2 infectivity has been investigated in vitro using RT-PCR SARS-CoV-2 positive samples incubated on Vero cells. One study proved that no positive culture was obtained using samples with Ct > 34[14]. It is known that severely immunocompromised patients, as those with hematologic malignancies, may shed replication-competent virus beyond 20 days. Prolonged shedding, of up to 151 days from symptom onset, and even multiple recurrences, have been documented[15]. Unfortunately, the detection of SARS-CoV-2 complementary DNA does not distinguish active replicating virus from residual nuclei acids.

In conclusion, patients with hematologic malignancies represent a special population at the highest risk of experiencing severe forms of CoViD-19. Ct was lower in those subgroups of patients with hematologic neoplasms who developed more severe forms of CoViD-19, which is consistent with the highest viral loads. Despite these results, we were not able to determine causality due to the small population studied. Ct deserves further study with larger cohorts in order to validate, or not, this quantitative laboratory determination which could be used as a course and infectivity prediction tool.

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