ISSN 1669-9106

ORIGINAL ARTICLE MEDICINA (Buenos Aires) 2021; 81: 536-545

CLINICAL CHARACTERISTICS AND EVOLUTION OF HEMATOLOGICAL PATIENTS AND COVID-19 IN ARGENTINA: A REPORT FROM THE ARGENTINE SOCIETY OF HEMATOLOGY

ANA L. BASQUIERA[1], **MERCEDES J GARCÍA**[1, 2], **JULIANA MARTINEZ ROLÓN**[3], **JULIETA OLMEDO**[2], **JULIA LAVIANO**[4], **RUBÉN BURGOS**[5], **GASTÓN CAEIRO**[1,2], **GUILLERMINA REMAGGI**[3], **PABLO RAÑA**[5], **MARIANO PAOLETTI**[6], **CARLOS M. GONZÁLEZ**[7], **ISOLDA FERNÁNDEZ**[8], **ASTRID PAVLOVSKY**[8], **MARIA A. PERUSINI**[9], **ANDREA RODRIGUEZ**[10], **LUCIANA GUANCHIALE**[1], **ANALIA CARVANI**[11], **LAURA MANDRILE**[11], **FLAVIA FIGUEROA**[12], **ÁNGELES VICENTE REPARAZ**[13], **PATRICIA N. FRAGAPANE MATHUS**[14], **GONZALO GARATE**[13], **MARÍA E. FAUQUE**[14], **GUSTAVO KANTOR**[15], **SOLEDAD CRUSET**[16], **JACQUELINE S. GONZALEZ LORCH**[15], **MILAGROS SZELAGOWSKI**[17], **MARÍA P. GIARINI**[18], **NATALIA OLIVEIRA**[19], **MARÍA C. GARCÍA**[20], **MARÍA V. VENTRIGLIA**[19], **PATRICIO H. PEREYRA**[19], **DANIEL R. GUTIERREZ**[20], **GUSTAVO KUSMINSKY**[21], **JOSEFINA TROCCOLI**[22], **MARÍA J. FREITAS**[19], **SANTIAGO CRANCO**[23], **NATALIA DEL V. SANCHEZ**[24], **IRENE REY**[22], **MARÍA E. FUNES**[25], **SOL JARCHUM**[26], **JULIAN FREUE**[27], **AUGUSTO MIROLI**[28], **OSVALDO GUERRERO**[29], **LISA LÓPEZ ARES**[30], **REINALDO CAMPESTRI**[27], **VICTOR BOVE**[31], **GRACIELA N. SALINAS**[24], **MARÍA CABREJO**[32], **JORGE H. MILONE**[17], **SOLEDAD ZABALJAUREGUI**[33], **DANIEL GOTTA**[34], **JUAN CARLOS DUPONT**[4], **GERMAN STEMMELIN**[35]

[1]Hospital Privado Universitario de Córdoba, [2]Hospital Raúl Ferreyra, Córdoba, [3]FUNDALEU, Buenos Aires, [4]CEMIC, Buenos Aires, [5]Conciencia-Instituto Oncohematológico de la Patagonia, [6]Clínica 25 de Mayo, Mar del Plata, Buenos Aires, [7]Clínica Privada Independencia, Munro, Buenos Aires, [8]Centro Pavlovsky, Buenos Aires, [9]Hospital Italiano de Buenos Aires, [10]Academia Nacional de Medicina, Buenos Aires, [11]Hospital Diego Paroissien, Isidro Casanova, Buenos Aires, [12]Hospital Néstor Kirchner, Tucumán, [13]Hospital Alemán, Buenos Aires, [14]Hospital Central de Mendoza, Mendoza, [15]Hospital Durand, Buenos Aires, [16]Hospital El Cruce, Florencio Varela, Buenos Aires, [17]Hospital Italiano de La Plata, [18]Hospital Houssay, Mar del Plata, [19]Hospital Nacional Posadas, El Palomar, Buenos Aires, [20]Hospital San Bernardo, Salta, [21]Hospital Universitario Austral, Pilar, Buenos Aires, [22]Hospital Ramos Mejía, Buenos Aires, [23]Instituto Alexander Fleming, Buenos Aires, [24]Rhesus Hematología, Mendoza, [25]Sanatorio Británico de Rosario, Santa Fe, [26]Sanatorio Allende, Córdoba, [27]Sanatorio Anchorena, Buenos Aires, [28]Sanatorio Franchin, Buenos Aires, [29]Sanatorio Sagrado Corazón, Buenos Aires, [30]Sanatorio Juan XXIII, Gral. Roca, Río Negro, [31]Instituto Oncohematológico Privado, Río Cuarto, Córdoba, [32]Sanatorio Municipal Julio Méndez, Buenos Aires, [33]Sanatorio de la Trinidad Ramos Mejía, Buenos Aires, [34]Hospital Urquiza, Concepción del Uruguay, Entre Ríos, [35]Hospital Británico, Buenos Aires, Argentina

Abstract Individuals with malignancies and COVID-19 have a lower survival compared with the general population. However, the information about the impact of COVID-19 on the whole hematological population is scarce. We aimed to describe the 30th day overall survival (OS) after COVID-19 infection in patients with a hematological disease in Argentina. A completely anonymous survey from the Argentine Society of Hematology was delivered to all the hematologists in Argentina; it started in April 2020. A cut-off to analyze the data was performed in December 2020 and, finally, 419 patients were reported and suitable for the analysis (average age: 58 years, 90% with malignant diseases). After the COVID-19 diagnosis, the 30-day OS for the whole population was 80.2%. From the entire group (419), 101 (24.1%) individuals required intensive care unit admission, where the 30-day OS was 46.6%. Among allogeneic stem cell transplant recipients, the 30-day OS was 70.3%. Factors associated with a low OS were two or more comorbidities, an active hematological disease and history of chemotherapy. In individuals with the three factors, the 30-day OS was 49.6% while the 30-day OS in those without those factors was 100%. Patients with hematological diseases have a higher mortality than the general population. This group represents a challenge and requires careful decision-making of the treatment in order not to compromise the chances of cure.

Key words: COVID-19, hematological patients, mortality, transplantation

Received: 8-III-2021 Accepted: 26-V-2021

Postal address: Ana Lisa Basquiera, Hospital Privado Universitario de Córdoba, Naciones Unidas 346, Barrio Parque Vélez Sarsfield, 5016 Córdoba, Argentina

e-mail: ana.basquiera@hospitalprivado.com.ar

Resumen ***Características clínicas y evolución de pacientes hematológicos y COVID-19 en Argentina: datos de la Sociedad Argentina de Hematología.*** El presente estudio tuvo por objetivo primario conocer la mortalidad de pacientes con enfermedad hematológica que presentaron infección por COVID-19 en Argentina. Para ello se difundió una encuesta desde la Sociedad Argentina de Hematología (SAH) entre los hematológos para informar sobre los pacientes con enfermedades hematológicas y diagnóstico de infección por SARS- CoV-2, entre el 19/4/2020, y el 7/12/2020. Se incluyeron individuos de todas las edades con diagnóstico de enfermedad hematológica benigna o maligna e infección por SARS-CoV-2 confirmada por técnica de RT-PCR. Se analizaron 419 pacientes (mediana 58 años; 90% enfermedades malignas). La supervivencia al día 30 fue de 80.2%. La supervivencia fue menor en aquellos que requirieron internación (74.2%), cuidados intensivos (46.6%) y asistencia respiratoria mecánica (36.8%). Entre los trasplantados alogénicos la supervivencia fue 70.3%. Los factores vinculados a la supervivencia global fueron las comorbilidades, el estado de la enfermedad al momento de la infección y el antecedente de quimioterapia. Se pudo establecer un *score* en el que aquellos que tuvieron un puntaje de 4 alcanzaron una supervivencia del 49.6% al día 30, mientras que la de los pacientes con *score* 0 fue del 100% a 30 días. En comparación con la población general, los pacientes con enfermedades hematológicas presentan una mayor mortalidad vinculada al COVID-19, motivo por el cual es primordial definir pautas destinadas a disminuir la exposición de los mismos sin comprometer las posibilidades de beneficiarse del tratamiento de la enfermedad de base.

Palabras clave: SARS-CoV-2, paciente hematológico, mortalidad, trasplante

KEY POINTS
Current knowledge

- Individuals with hematological diseases have a variable immunocompromise because of the disease itself and the treatment they need. These patients have a higher morbidity and mortality by SARS-CoV2 than general population.

Contribution of the article to the knowledge

- In a population of 491 individuals with hematological diseases and SARS-CoV2 infection, the mortality at day 30 was 20.8% and raised to 63.2% in patients requiring mechanical ventilation.
- Factors associated with inferior overall survival were: comorbidities, status of hematological disease at coronavirus infection and a history of chemotherapy.

In December 2019, an outbreak of a respiratory illness caused by a new coronavirus was detected in China. This virus was called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). This new type of respiratory disease (COVID-19) is characterized by the high human-human transmission[1]. On January, 30th 2020, the Chief Executive Officer (CEO) of the World Health Organization (WHO) declared that the outbreak of the new coronavirus represented a public health emergency and on March, 11th 2020, it was declared a pandemic by the WHO[2]. To date, 88 387 352 worldwide cases have been confirmed and there have been 1 919 204 deaths caused by COVID-19[3]. In Argentina, there were 1 703 352 number of cases and 41 273 deaths from COVID-19 until December, 16th 2020. The first identified case in the country was in March, 3rd 2020[3, 4].

The Italian National Institute reported a case fatality rate of 7.2%, based on 22 512 cases. These deaths were mainly observed in old, male patients with multiple comorbidities; of this series, the 20% of the deceased were cancer patients[5]. A meta-analysis of 22 studies reported a mortality of 21.1% in cancer patients[6]. On the other hand, adult patients with hematological malignancies have a higher mortality due to COVID-19 than the general population[7]. These numbers have been variable: between 14% and 36% depending on the characteristics of the disease and the geographic location of the published series[8-14].

Since the beginning of the pandemic, recommendations have been issued by different scientific societies. The aim is to reduce the probability of infection and death by COVID-19 in patients with hematological and oncological pathologies, based on the immunosuppression that these individuals have and which is due to their underlying pathology and the treatments they receive[15-21]. The negative impact of the treatments could depend on the corresponding diagnosis, but patients with hematological malignancies constitute, in turn, a group with potential worsening of the disease due to the delay or the lack of a timely treatment. Thus, in pandemic times a careful balance of the risk and benefit of a specific treatment must be considered[22, 23].

In Argentina, in 2009, during the Influenza A (H1N1) epidemic, the incidence of pneumonia among patients with neoplasms was 66%, and the mortality was 18%[24]. Therefore, it is a priority to know the clinical characteristics and the evolution of patients with hematological pathologies in Argentina to establish guidelines for the care and treatment of these individuals. The Argentine Society of Hematology has designed a survey to know the geographical distribution and the clinical characteristics of SARS-CoV2 infection in patients with hematological diseases in our country. The primary objective of the present study was to evaluate the survival at day 30 of patients with hematological diseases and who tested positive for SARS- CoV2; and the secondary objectives were: (i) to describe the clinical symptoms, the underlying diagnosis,

the comorbidities and the treatment of the underlying pathology of patients with SARS-CoV2 infection; (ii) to determine the factors linked with the deaths caused by COVID-19; (iii) to determine the need of hospitalization in an intensive care unit (ICU) and invasive mechanical ventilation (IMV) in this patient population.

Materials and methods

A survey was designed through an electronic form by the first author. The survey input began on 04/19/2020 and the data analysis was made on 12/7/2020. This survey was retrospective since it had to be completed at least 30 days after diagnosing SARS-CoV2 infection. All national specialists in Hematology were invited to participate through the Argentine Society of Hematology.

The eligibility criteria were: patients of all ages with a diagnosis of a benign or malignant hematological pathology and SARS-CoV2 infection confirmed by PCR technique. Those cases that had a data absence about the patient evolution were excluded. Among the variables studied, death from COVID-19 - according to WHO - was included as a result variable: death resulting from a disease clinically suitable with a probable or confirmed case, unless there was a clear alternative cause of death that could not be related to the disease due to COVID-19, and there should not be a complete recovery period between the disease and the death. It was also included as an exposure variable: confirmed COVID-19 infection. In relation to the demographic variables and patient data, the following items were included: patient initials, age at the time of diagnosis of SARS-CoV2 infection, gender, province of origin, diagnosis of hematological pathology, date of diagnosis of hematologic pathology, disease status at the time of SARS-CoV2 infection (remission, active disease), comorbidities (smoking, asthma, diabetes, high blood pressure, obesity, chronic obstructive pulmonary disease, solid tumor, heart failure, ischemic heart disease, arrhythmia, chronic kidney failure, stroke, liver cirrhosis, autoimmune diseases, history of chemotherapy, date of the last cycle and scheme received, history of hematopoietic stem cell transplantation (SCT) (autologous/allogeneic) and date of SCT. Regarding the SARS-CoV2 infection, the variables were: symptoms, date of onset of symptoms, presence of fever, cough, odynophagia, dyspnea, diarrhea, evidence of other symptoms, pneumonia, computed tomography, bronchoalveolar lavage, coagulopathy, hospitalization requirement, date of admission to hospitalization, discharge date, need for ICU, mechanical respiratory assistance requirement, treatment received (hydroxychloroquine/azithromycin-lopinavir/ritonavir-steroids- others), death and date of death or last update.

The continuous variables are presented as median and interquartile range (IQR) and were compared using the Mann Whitney test. The categorical variables are presented as relative frequencies and percentages; also, the chi-square test or Fisher's exact were used for comparisons. The overall survival (OS) was analyzed using Kaplan-Meier curves and compared using the log-rank test. For the univariate and multivariate comparisons, the respective unadjusted and adjusted HR were obtained through COX regression, with their respective 95% confidence intervals (95% CI). Factors with a p value of less than 0.05 in the univariate were entered in the multivariate analysis performing Cox regressions to obtain the final model. The statistical significance was defined as a p value <0.05 and the statistical analysis was carried out using the Easy R statistical program Easy R[25].

The study was carried out in full accordance with the current national and international regulations: Declaration of Helsinki of the World Medical Association in its most updated version, resolution 1480/2011 of the National Ministry of Health and the Law 25326 on Protection of Personal Data. All the study data was treated with the utmost confidentiality and anonymously, with restricted access only for the authorized personnel for the purposes of the study and, once more, in accordance with the regulations above mentioned. The study was approved by the *Comité Institucional de* Ética *de Investigación en Salud* (Health Research Ethics Committee) of the Hospital Privado Universitario de Córdoba.

Results

There were 428 response forms received, and 9 of them were duplicated, so they were excluded. This leaves 419 cases suitable for analysis.

The cases were registered between 04/19/2020 and 12/07/2020. The vast majority of them belonged to Buenos Aires Province (n = 135) and to the Autonomous City of Buenos Aires (n = 128), this was followed by the provinces of Córdoba (n = 38) and Mendoza (n = 34) (Fig. 1). The demographic characteristics and comorbidities are expressed in Table 1.

Fig. 1.– Number of reported cases in each province of the Argentine Republic

TABLE 1.– *Patients characteristics at the moment of COVID-19 diagnosis*

Variable	Results
Age, average (IQR)	58 (41.5-68)
Gender, male/female	233/186
Baseline diagnosis, benign disease/malignancy	36/383
Baseline disease, number (%)	
Autoimmune hemolytic anemia	3 (0.7)
Amyloidosis	2 (0.5)
Anemia	2 (0.5)
Anticoagulation	9 (2.1)
Aplastic anemia	8 (1.9)
Gaucher disease	2 (0.5)
Paroxysmal nocturnal hemoglobinuria	1 (0.2)
Large granular lymphocyte leukemia	2 (0.5)
Hodgkin lymphoma	32 (7.6)
Acute lymphoblastic leukemia	44 (10.5)
Chronic lymphocytic leukemia	26 (6.2)
Acute myeloid leukemia	47 (11.2)
Chronic myeloid leukemia	24 (5.7)
Non-Hodgkin lymphoma	100 (23.9)
Monoclonal gammopathy of undetermined significance	9 (2.1)
Multiple myeloma/plasma cell leukemia	59 (14.1)
Idiopathic thrombocytopenic purpura	9 (2.1)
Myelodysplastic syndrome	26 (6.2)
Philadelphia-negative chronic myeloproliferative neoplasms	14 (3.3)
≥ 2 Hematological diseases, number (%)	16 (3.8)
Active disease / Remission	259/160
Treatment antecedent, number (%)	
Chemotherapy	301 (71.8)
Hematopoietic transplant, autologous/allogeneic	34 (8.1)/19 (4.5)
Anti-CD20	80 (19.1)
TKI	20 (4.8)
Comorbidities, number (%)	
Patients with 1 or more	231 (55.1)
Median, range	1 (1-7)
Arterial hypertension	95 (22.7)
Obesity	66 (15.7)
Smoker - Former smoker	61 (14.5)
Diabetes	46 (11)
Heart failure / coronary disease	38 (9.1)
Pulmonary disease	19 (4.5)
Solid tumor	15 (3.6)
Autoimmune disease	12 (2.9)

IQR: interquartile range; TKI: tyrosine kinase inhibitors

In reference to the clinical data and the disease due to COVID-19, it was observed that the majority of the 419 patients studied had a diagnosis of hematological malignancies (n = 383; 91.4%). The most frequent diagnoses were non-Hodgkin lymphoma, acute leukemia, and multiple myeloma/monoclonal gammopathies (Table 1). The average age was 58 years old; only seven (1.7%) cases younger than 18 years old were registered, 306 were older than 40 years old (73%) and 92 (21.9%) were older than 70 years.

From the 419 assessable patients, 358 had symptoms (85.4%). The most frequent symptom was fever. In addition, the following syndromes associated with COVID-19 were described: idiopathic thrombocytopenic purpura (n = 1), hemolytic anemia (n = 3), coagulopathy (n = 4) and deep vein thrombosis (n = 10). More than half of the patients required hospitalization (n=272, 64.9%) and 101 were hospitalized in ICU (24.1%) (Table 2). A variety of treatments were reported and the most common one was dexamethasone (Table 2).

TABLE 2.– *Symptoms due to COVID-19 and treatments received*

Variable	Results
Symptoms	
Fever	310
Tos	197
Dispnea	120
Odynophagia	54
Headache	40
Diarrhea	34
Asthenia/fatigue	29
Anosmia	26
Myalgia	22
Rhinorrhea	8
Otitis	1
Ageusia	3
Trigeminal neuralgia	1
Hospital admission, number (%)	272 (64.9)
Chest CT scan done, number (%)	273 (65.1)
Bronchoalveolar lavage, number (%)	19 (4.5)
Pneumonia, number (%)	230 (54.9)
ICU admission, number (%)	101 (24.1)
Invasive mechanical ventilation, number (%)	75(17.9)
COVID-19 treatments, number	
Hydroxychloroquine	2
Azithromycin	46
Antivirals	10
Methylprednisolone	33
Dexamethasone	107
COVID-19 convalescent plasma	60
Ruxolitinib	1
Intravenous immunoglobulin	2

**CT: computed tomography; ICU: intensive care unit*

Of the total number, 87 patients died in an average of 16 days (range 0-100). The overall survival (OS) at day 30 was 80.2% (95% CI 75.6-84) (Fig. 2). Patients hospitalized for COVID-19 had an OS at day 30 of 74.2% (95% CI 67.9-79.5). Those who were admitted to the ICU had an OS at day 30 of 46.6% (95% CI 36.2-56.3). Those 75 cases who required IMV, the 30-day OS was 36.8% (95% CI 25.8-47.8). The 30-day OS of patients with malignancies and benign diseases was 80.6% (95% CI 75.9-84.6) and 84.8% (95% CI 67.2-93.4) (p = 0.257), respectively. The mortality data due to disease is shown in Table 3; it excludes those with an allogeneic stem cell transplanta-

Fig. 2.–Survival after COVID-19 diagnosis in patients with hematological diseases

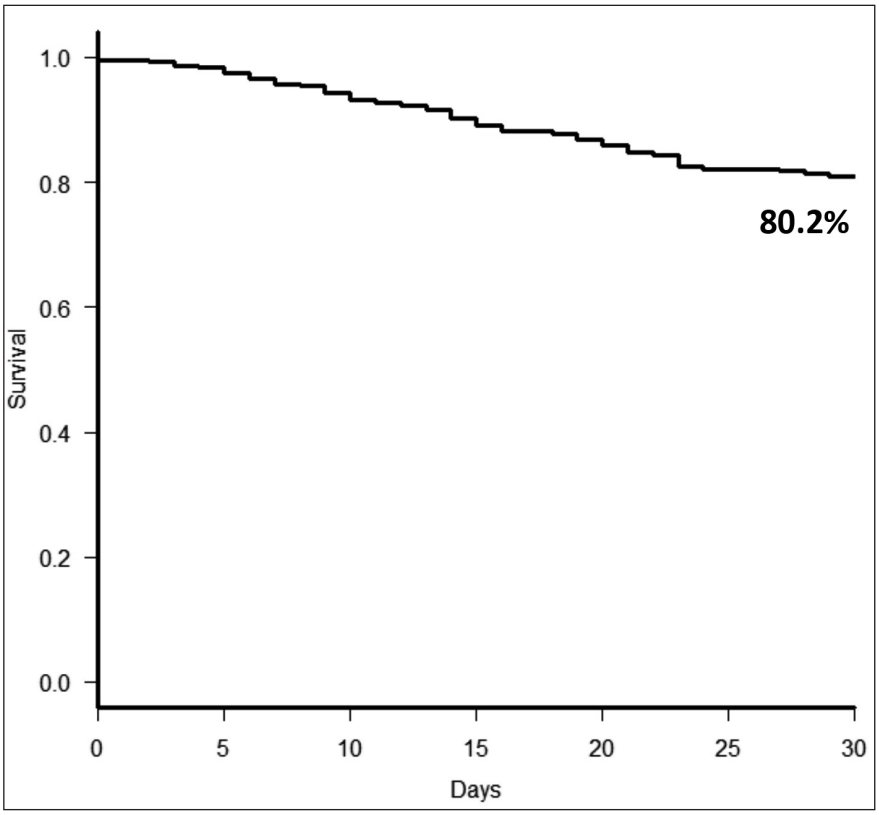


TABLE 3.– *Survival according to the diagnosis (patients with a history of allogeneic transplant were excluded)*

Diagnosis	Number events/ evaluable	30 day - Overall survival (95% CI)
Acute myeloid leukemia	12/39	70.8 (52.2-83.3)
Plasma cell neoplasms	16/70	74.1 (60.9-83.4)
Acute lymphoblastic leukemia	12/39	78.5 (59.7-89.3)
Chronic myeloid leukemia*	5/22	78.7 (52.6-91.5)
Philadelphia-negative chronic myeloproliferative neoplasms	2/13	79.1 (36.7-94.7)
Myelodysplastic syndrome	3/24	80.8 (50.3-93.6)
Hodgkin's lymphoma	5/32	82.1 (61.9-92.2)
Benign hematologic disease	6/35	84.3 (66.2-93.2)
Chronic lymphocytic leukemia	4/26	86.4 (63.4-95.4)
Non-Hodgkin´s lymphoma	17/102	89.4 (81.2-94.2)

CI: confidence interval

**3 out of 5 patients presented with a blastic phase at the moment of COVID-19*

tion (SCT). The factors linked with the OS in the univariate analysis were: age, the presence of comorbidities, the disease state at the time of SARS-CoV-2 infection and the history of chemotherapy.

Except for age, the remaining variables retained their statistical significance in the multivariate model ($p < 0.05$): the presence of two or more comorbidities (HR 2.271), an antecedent of previous chemotherapy (HR 2.548) and the presence of active hematological disease (HR 3.104) (Table 4). Afterwards, an index was constructed to predict survival at day 30 considering these significant parameters, awarding one point to the variables two or more comorbidities and an antecedent of chemotherapy, and two points to the presence of active disease, according to the adjusted HR. Mortality was similar between those groups with one and two points, so four groups were individualized with a significant difference in the overall survival at day 30 ($p < 0.001$): 0 points (n = 21; 100%); 1-2 points (n = 201; 87.5%; 95% CI 81.4 - 91.7); 3 points (n = 152; 76.1%; 95% CI 67.3 - 82.8); and 4 points (n = 45; 49.6%; 95% CI 32.8 - 64.2); (Fig. 3).

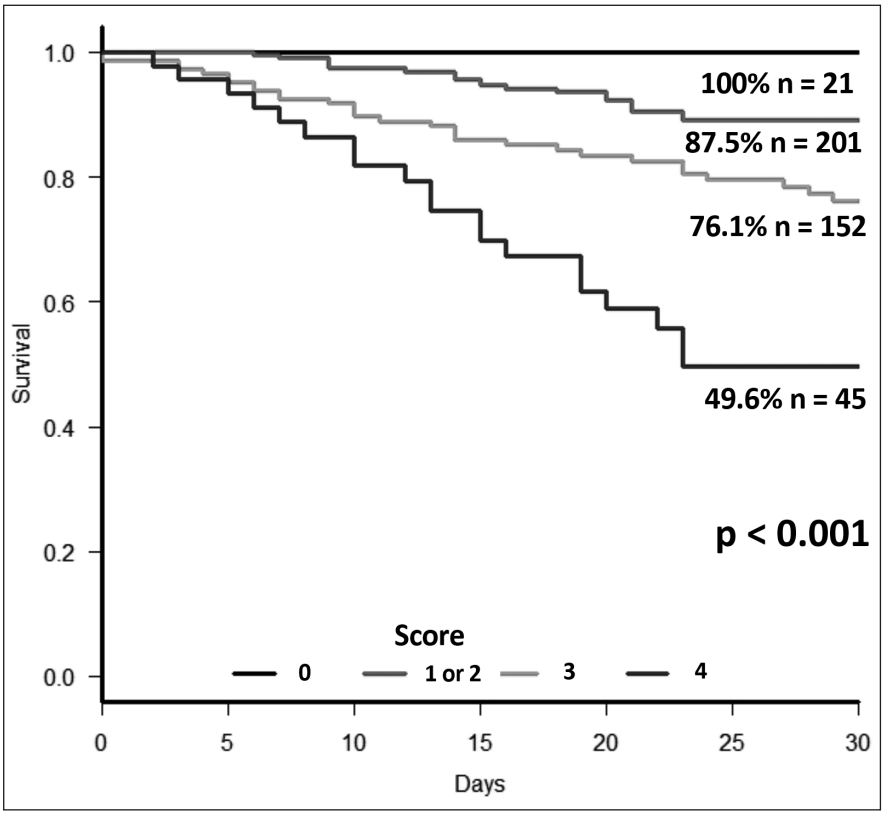
There were 19 registered patients who had COVID-19 infection after a SCT (average age 49 years old; IQR 36-53): 10 with identical related donors, six with partially

TABLE 4.– *Factors associated with survival at day 30 after COVID-19 infection (n = 419)*

Variable	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age, continuous (1-1,025)	1.013	0.051 -		
Age,				
< 60	Ref.	0.041	Ref.	0.084
≥ 60	1.553 (1.018-2.371)		1.474 (0.948-2.291)	
Gender				
Female	Ref.	0.053	-	
Male	1.547 (0.994-2.415)			
Comorbidities, continuous	1.339 (1.167-1.535)	< 0.001	-	
Comorbidities				
0-1	Ref.	< 0.001	Ref.	< 0.001
2 or more	2.239 (1.459-3.434)		2.271 (1.479-3.488)	
Hematological disease				
Benign	Ref.	0.201	–	
Malignancy	1.925 (0.705-5.250)			
Disease status				
In remission	Ref.	< 0.001	Ref.	< 0.001
Active	2.717 (1.632-4.524)		3.104 (1.854-5.197)	
Chemotherapy				
No	Ref.	0.015	Ref.	
Yes	1.967 (1.143-3.385)		2.548 (1.472-4.412)	< 0.001
Anti-CD20				
No	Ref.	0.443	–	
Yes	0.799 (0.451-1.417)			

CI: confidence interval; HR: hazard ratio

Fig. 3.– Survival after COVID-19 diagnosis according to the prognosis factors (p < 0.001)



identical related donors and 3 with unrelated donors. In five of the 19 cases, the SCT was performed during the 2020. Of those 19 patients, 15 presented symptoms and 14 required hospitalization: six in ICU and five required IMV. The 30-day OS was 70.3% (95% CI 30.1-80.7). Regarding the six deaths, two of them presented a septic shock, one also presented other transplant complications - such as veno- occlusive disease and graft failure - one presented a relapse of the disease and another patient had severe COVID-19 in the context of chronic graft versus host disease (GVHD). All the deceased patients were receiving immunosuppression at the time of COVID-19 disease (Table 5).

Discussion

We present the data of 419 patients with a hematological pathology and who had COVID-19 in Argentina. The average age of the individuals was 58 years old, the average number of comorbidities was one, the majority had a diagnosis of malignancy, the majority were under an active treatment at the time of the infection and there were 14.6% (n = 61) asymptomatic patients reported. The mortality at day 30 was 20.8%. The most important adverse factors linked with survival after COVID-19 were: comorbidities, chemotherapy treatment, and active disease at the time of the infection.

Several groups presented the data and the evolution of COVID-19 in the hematological population. The ASH Research Collaborative COVID-19 Registry for Hematology reported data from 250 cases with a malignant hematological pathology, 78% of them were older than 40 years and 36% were older than 70 years. In those series, only the 3% were asymptomatic, 54% was hypertensive, 33% were diabetic, and 25% were smokers or ex-smokers. Moreover, the most frequent malignancy was acute leukemia. The mortality of patients with moderate to severe COVID-19 who required hospitalization was 28% and increasing to 42%[9, 10]. Our series differ from ASH's in terms of the proportion of asymptomatic cases, the superior proportion of comorbidities and the inferior mortality, probably because we included patients with all types of hematological pathologies and a younger population. The series published by the Italian Hematology Alliance on COVID-19 registered a number of 536 patients with COVID-19 and who also had hematological neoplasms (average age 68 years old; average comorbidities: four);

TABLE 5.– *Patients with COVID-19 after allogeneic transplant (n = 19)*

Variable	Alive n = 13	Death n = 6	p value
Age, average (IQR), and / or	44 (34-52)	49.5 (44.2-54)	0.253
On immunosuppression			
Yes	5	6	0.018
No	8	0	
Year of transplantation			
2019-2020	5	6	0.018
Others	8	0	
Comorbidities			
-1	12	4	0.222
2 or more	1	2	
GVHD			
Yes	3	1	1.000
No	10	5	

IQR: interquartile range; GVHD: graft versus host disease

the mortality of the whole group was 37%[7]. Despite being older and comorbid individuals, the mortality of those admitted to the ICU was 63%[7], similar to the one in our series. The *Asociación Madrileña de Hematología y Hemoterapia* [The Madrid Association of Hematology and Hemotherapy] analysed data of 697 patients with hematological malignancies (average age 72 years). In 62% of the cases, COVID-19 disease was severe / critical in 62% and mortality was 33%[8]. Like in our series, the presence of more than two comorbidities was associated with a higher mortality. Other significant factors were the diagnosis of acute myeloid leukemia (AML) and active treatment with monoclonal antibodies, while chronic myeloproliferative neoplasms and the treatment with hypomethylating agents were associated with a lower mortality[8].

Considering the mortality due to disease, we found that acute leukemias and plasma cell neoplasms were associated with higher mortality. This observation was made by other authors[8]. Of the group of patients with plasma cell neoplasm, 16 out of 70 died due to COVID-19 (22.8%). In the series by Chari et al. and according to the International Myeloma Society, of 650 individuals with multiple myeloma (average 69 years old), 33% died after the infection with SARS-CoV2, although the geographic variability was very high and the mortality ranged from 27% to 57%. The factors associated with higher probability of death were: age, high-risk myeloma, renal involvement and suboptimal myeloma control; the history of autologous SCT had no impact[22]. In the UK series, the mortality reached 54.6% in patients with symptomatic myeloma and who were under systemic treatment at the time of SARS-CoV2 infection[26].

In individuals with Philadelphia negative myeloproliferative neoplasms, the mortality in our series was 15.4%, which is lower than the 28.6% reported in the series by Barbui et al. (n = 175), probably due to the higher number of cases in this series[27]. Several authors found that patients in the chronic phase of chronic myeloid leukemia (CML) and who were receiving treatment with tyrosine kinase inhibitors were not at an increased risk of getting COVID-19 infection or death[28-30]. In the group of Argentine patients with CML, five out of 24 cases died. However, three of them were in the blastic phase and two in the chronic phase had four and three comorbidities, respectively. Our series also included 36 individuals with a benign hematological pathology; five deceased cases were in this group. Few series included patients with benign hematological diseases. Fox et al. studied 55 hematological patients with COVID-19. In this series, three cases had a benign pathology and one of them died from COVID-19[9, 10].

Of the 419 patients included in our study, 19 had a history of allogeneic SCT and, in this group, the mortality was higher than in the whole cohort since it was 30% at day 30. All the cases that died were transplanted in the years 2019 and 2020 and were under immunosuppressive agents at the moment of the infection. The data about the impact of COVID-19 in the context of SCT is variable. Researchers at the Memorial Sloan Kettering Cancer Center studied 77 individuals who received cell therapy (allogeneic, autologous, and CAR-T transplantation) and who also had SARS-CoV2 infection. The overall mortality of hospitalized patients with an active malignancy was 41% and of hospitalized patients without an active malignancy was 21%. The comorbidities were another determining factor of evolution. Antibodies against SARS-CoV2 after infection were developed in 66% of the cases[31]. Sultan et al., described seven cases with a history of allogeneic SCT

and who had SARS-CoV2. All of these were in complete remission and receiving immunosuppression, and 3 of them had GVHD. There was no mortality from COVID-19 in that series[32]. The Spanish group also found a lower mortality in SCT recipients than in non-SCT[33]. In contrast, a mortality of 43% was reported by Kanellopoulus et al. in another series of seven allogeneic SCT recipients[34]. The 30-day overall survival of 70% in our cohort is similar to a recent CIBMTR report with 318 transplanted patients with COVID-19, and to the Italian and North American cohorts[7, 31, 35, 36]. In the CIBMTR report, at 30 days after the diagnosis of COVID-19, the overall survival was 68% for recipients of allogeneic SCT and 67% for recipients of autologous SCT. On the one hand, among the allogeneic SCT recipients, the factors associated with a poor outcome were: 50 years old or older, male sex and the development of COVID-19 within 12 months of transplantation[36]. On the other hand, among the autologous SCT recipients, a disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma[36].

The impact of COVID-19 in the present study was assessed in terms of hospitalization and mortality. However, other factors that may impact survival of this population were not assessed. In the study by Albiges et al., 178 cancer patients managed at the Gustave Roussy Cancer Center were studied; of them, 17.8% were hematological patients. Mortality was 17.4%, the average delay in cancer treatment was 20 days in 41% of the cases, and the therapeutic strategy had to be adapted to the clinical situation of the patient in 30% of the cases[37].

Within the treatments used against COVID-19, in our cohort, most of the cases received steroids. Only the 11% received azithromycin and 0.5% hydroxychloroquine compared with ASH's registry that showed 50% y 64% respectively[9]. It is important to know that to date, no standard treatment has been established for immunosuppressed individuals with COVID-19.

One of the main limitations of our study resides in the fact that it is a collaborative registry, so there might be an interobserver variability and, as the treatments are not standardized, there may be an impact on the patient's clinical results which may constitute a bias. However, we consider that the data obtained provides knowledge about the impact of an emerging pathology in our population, thus making it possible to evaluate those results that can modify screening COVID-19 and treatment decisions. Our survey allows us to demonstrate the greater severity of SARS-CoV2 infection in hematological patients and to identify the clinical variables associated with a worse evolution. As a consequence, in order to reduce the morbidity and mortality of patients with hematological diseases, some prevention methods should be considered; the most important one is to reduce the risk inside the hospital and the exposure outside it and to insist on the education about the use of masks, hand washing and distancing.

Acknowledgments: The authors thank the hematologists of the Argentine Society of Hematology who provided data to carry out this study and the following institutions reporting: Academia Nacional de Medicina; CEMIC; Centro de Especialidades Médicas Neuquén; Centro de Hematología Pavlovsky; Clínica 25 de mayo, Mar del Plata; Clínica Privada Independencia Munro; Colegiales; Conciencia Instituto Oncohematológico Neuquén; Consultorios Hematológicos; Diagnóstico Centro Médico; Consultorio Dra Ríos Part; FUNDALEU; HIGA Diego Paroissien; Hospital Italiano de Buenos Aires; Hospital Kirchner; Hospital Alemán; Hospital Álvarez; Hospital Aramburu; Hospital Británico; Hospital Central de Mendoza; Hospital Cirilo Sanguinetti; Hospital Durand; Hospital El Cruce; Hospital Español de La Plata; Hospital Houssay Mar del Plata; Hospital Italiano de La Plata; Hospital Italiano Mendoza; Hospital Iturraspe; Hospital Kirchner; Hospital Marcial Quiroga; Hospital Oncológico José C Paz; Hospital Posadas; Hospital Privado Universitario de Córdoba; Hospital Raúl Ferreyra de Córdoba; Hospital San Bernardo, Salta; Hospital Tornú; Hospital Universitario Austral; Hospital Ramos Mejía; IADT; Instituto Alexander Fleming; Instituto Lanari; Instituto Oncohematológico Privado SRL, Río Cuarto; Leben Salud; Marta Zerga consultorio; Hospital Méndez; Puentes Salud; Rhesus Hematología; Sanatorio Británico Rosario; Sanatorio Allende Córdoba; Sanatorio Anchorena; Sanatorio de la Trinidad Ramos Mejía; Sanatorio Delta Santa Fe; Sanatorio Franchin; Sanatorio General Sarmiento; Sanatorio Güemes; Sanatorio Juan XXIII; Sanatorio Mapaci; Sanatorio Mayo; Sanatorio Modelo de Quilmes; Sanatorio Municipal Julio Méndez; Sanatorio Sagrado Corazón; Clínica del Valle, Comodoro Rivadavia; SMQ, Sanatorio de la Trinidad Palermo.

Conflict of interest: None to declare

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; 395: 470-3.
2. World Health Organization. Coronavirus disease (COVID-19) pandemic. Situation Reports. In: *https: //www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf*; accessed February 2021.
3. World Health Organization. World Health Organization. (2021). COVID-19 weekly epidemiological update, 12 January 2021. In: *https: //apps.who.int/iris/handle/10665/338703;* accessed February 2021.
4. Argentina. Ministerio de Salud. Salud confirma el primer caso de coronavirus en el país. 3 Mar 2020. In: *https: // www.argentina.gob.ar/noticias/salud-confirma-el-primer-caso-de-coronavirus-en-el-pais;* accessed February 2021.
5. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020; 323: 1775-6.
6. ElGohary GM, Hashmi S, Styczynski J, et al. The risk and prognosis of COVID-19 infection in cancer patients: A systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther* 2020; S1658-3876: 30122-9.
7. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19

severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol* 2020; 7: e737-45.
8. García-Suárez J, de la Cruz J, Cedillo Á, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. *J Hematol Oncol* 2020; 13: 133.
9. Wood WA, Neuberg DS, Thompson JC, et al. Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. *Blood Adv* 2020; 4: 5966-75.
10. Fox TA, Troy-Barnes E, Kirkwood AA, et al. Clinical outcomes and risk factors for severe COVID-19 in patients with haematological disorders receiving chemo- or immunotherapy. *Br J Haematol*. 2020; 191: 194-206.
11. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: A systematic review and meta-analysis of 3377 patients. *Blood* 2020; 136: 2881-92.
12. Yigenoglu TN, Ata N, Altuntas F, et al. The outcome of COVID-19 in patients with hematological malignancy. *J Med Virol* 2021; 93: 1099-1104.
13. Borah P, Mirgh S, Sharma SK, et al. Effect of age, comorbidity and remission status on outcome of COVID-19 in patients with hematological malignancies. *Blood Cells Mol Dis* 2021; 87: 102525.
14. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant* 2020; 55: 2180-4.
15. Algwaiz G, Aljurf M, Koh M, et al. Real-World Issues and Potential Solutions in Hematopoietic Cell Transplantation during the COVID-19 Pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee. *Biol Blood Marrow Transplant* 2020; 26: 2181-9.
16. Provencio M, Ruano-Raviña A. How we treat patients with lung cancer during the SARS-CoV-2 pandemic. *ESMO Open* 2020; 4(Suppl 2): e000785.
17. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. *Oncologist* 2020;25: e936-45.
18. The Lancet Oncology. COVID-19: global consequences for oncology. *Lancet Oncol* 2020; 21: 467.
19. Subspecialty Group of Hematology and Oncology, Society of Pediatrics of Hubei. Standardized management guideline for pediatric wards of hematology and oncology during the epidemic of coronavirus disease 2019. *Zhongguo Dang Dai Er Ke Za Zhi* 2020; 22: 177-82.
20. Cabero-Martínez A, Sánchez-Guijo F, López-Corral L, et al. Measures to Maintain a SARS-CoV-2 Negative Inpatient Hematological Unit in the Midst of the COVID-19 Pandemic. *Front Med (Lausanne)* 2020; 7: 462.
21. Wilde L, Isidori A, Keiffer G, Palmisiano N, Kasner M. Caring for AML Patients During the COVID-19 Crisis: An American and Italian Experience. *Front Oncol* 2020; 10: 1689.
22. Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood* 2020;136: 3033-40.
23. Gavillet M, Carr Klappert J, Spertini O, Blum S. Acute leukemia in the time of COVID-19. *Leuk Res* 2020; 92: 106353.
24. Dignani MC, Costantini P, Salgueira C, et al. Pandemic 2009 Influenza A (H1N1) virus infection in cancer and hematopoietic stem cell transplant recipients; a multicenter observational study. *F1000Res* 2014; 3: 221.
25. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; 48: 452-8.
26. Cook G, John Ashcroft A, Pratt G, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. *Br J Haematol* 2020;190: e83-6.
27. Barbui T, Vannucchi AM, Alvarez-Larran A, et al. High mortality rate in COVID-19 patients with myeloproliferative neoplasms after abrupt withdrawal of ruxolitinib. *Leukemia* 2021; 35: 485-93.
28. Breccia M, Abruzzese E, Bocchia M, et al. Chronic myeloid leukemia management at the time of the COVID-19 pandemic in Italy. A campus CML survey. *Leukemia* 2020; 34: 2260-1.
29. Cakir B. Outcome of COVID-19 in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors. *J Oncol Pharm Pract* 2020; 26: 2068-9.
30. Ector GICG, Huijskens EGW, Blijlevens NMA, Westerweel PE. Prevalence of COVID-19 diagnosis in Dutch CML patients during the 2020 SARS-CoV2 pandemic. A prospective cohort study. *Leukemia* 2020; 34: 2533-5.
31. Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest* 2020;130: 6656-67.
32. Sultan AM, Mahmoud HK, Fathy GM, Abdelfattah NM. The outcome of hematopoietic stem cell transplantation patients with COVID-19 infection. *Bone Marrow Transplant* 2020; 56: 971-3.
33. Piñana JL, Martino R, García-García I, et al. Risk factors and outcome of COVID-19 in patients with hematological malignancies. *Exp Hematol Oncol* 2020; 9: 21.
34. Kanellopoulos A, Ahmed MZ, Kishore B, et al. COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience. *Br J Haematol* 2020; 190: e67-70.
35. Varma A, Kosuri S, Ustun C, et al. COVID-19 infection in hematopoietic cell transplantation: age, time from transplant and steroids matter. *Leukemia* 2020; 34: 2809-12.
36. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol* 2021; 8: e185-93.
37. Albiges L, Foulon S, Bayle A, et al. Determinants of the outcomes of patients with cancer infected with SARS-CoV-2: results from the Gustave Roussy cohort. *Nature Cancer* 2020; 1: 965-75.