Received: 8 June 2020 | Revised: 4 July 2020 | Accepted: 14 July 2020

DOI: 10.1111/ijlh.13301

ISLH International Journal of Laboratory Hematology WILEY

LETTER TO THE EDITOR

COVID-19 in patients with hematological malignancies: A retrospective case series

Dear Editors,

Spain, with more than 249.000 cases and 28.363 deaths as of July 1st, 2020, has one of the highest burdens of coronavirus disease 2019 (COVID-19) worldwide.[1]

Since its first identification in China in December 2019, several reports have been published describing epidemiological and clinical characteristics of patients with COVID-19, with an overall mortality rate ranging from 1.4% to 2.3%, that can increase up to 22.4%-24.5% in hospitalized patients.[2,3]

Patients with cancer have a higher susceptibility to infections due to their immunosuppression state caused by the malignancy itself or by antineoplastic treatments. Specifically, infections caused by community respiratory viruses had been associated with poor outcome in patients with hematological malignancies. Few data are available on hematologic patients and COVID-19 infection, with discordant results, probably due to the small sample size of the studies. To date, these data come from retrospective clinical case series[4-9] from different countries in which case fatality rates (CFR) range from 33% to 62%. Mortality has been associated, depending on the published series, with age, comorbidities, active hematological disease, intensive treatment, or some laboratory variables.

Thus, more data are required to better characterize the real impact of COVID-19 in patients with hematological neoplasms, in order to optimize clinical decision-making.

We carried out a single-center analysis of 41 consecutive patients with hematological malignancies who developed COVID-19 between March 8 and April 8, 2020 at University Hospital Infanta Leonor, Madrid.

Cases were defined as COVID-19 by clinical, laboratory, and imaging criteria defined elsewhere.[10] A nasal swab SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) test confirmed clinical suspicion in 38/41 cases. The remaining three patients, who tested PCR negative, were diagnosed with COVID-19 on clinical grounds.

We studied the likely transmission source, comorbidities, hematological disease status, clinical and laboratory characteristics of the COVID-19 episode, its severity, rate of progression to acute respiratory distress syndrome (ARDS), and development of thrombotic events. We analyzed the CFR and the clinical and laboratory factors influencing mortality. Finally, we looked into time to SARS-CoV-2 PCR clearance, aiming to see if it was different from published data on nonhematological or cancer patients.

Statistical analysis was performed using SPSS 21.0 software package (SPSS). The Mann-Whitney test was done to compare quantitative variables. Odds ratio for mortality was calculated by logistic regression. Cox regression was used for univariate analysis of the impact of variables on overall survival (OS). These data were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). A P-value $< .05$ was considered significant for all analyses. The local ethics committee approved the study (R 027-20).

The source of transmission was unknown in 4/41 (10%) cases. Seven patients (17%) declared a direct contact with a COVID-19 positive family member. Nosocomial transmission was confirmed in 5/41 (15%) as they had been admitted for other reasons prior to the outbreak, and seemed likely in 25/41 patients (61%) who had attended the hematology day hospital in the previous 14 days. These patients had been advised to go to the day hospital to receive blood products or due to a new hematological diagnosis or uncontrolled disease requiring therapy. The French group described a similar incidence of nosocomial COVID-19 in hematological patients.[6]

Complete details of the entire cohort are shown in Table 1. The median age of patients was 76 years old (range, 37-92) and 53% were male. Most of them (70%, n = 29) had a lymphoid malignancy. Patients had previously received a median of one (range, 0-5) line of treatment for their hematological disease. Half of the patients (51%, 21/41) were under active treatment at the time of COVID-19. None of the patients had undergone a previous hematopoietic stem cell transplantation (HSCT). All patients but three (93%) had additional chronic medical conditions. The median duration of symptoms before the SARS-CoV-2 PCR assay was performed was 5.6 (range 0-18) days.

Twenty-nine (70%) patients required hospitalization due to the severity of COVID-19, while 6 (15%) were treated as outpatients.

The severity of pneumonia according to WHO criteria was severe for the majority of the patients (73%, n = 30) and mild for the rest (15% n = 6). Only 5/41 (12%) patients developed ARDS, and all of them died despite ICU admission.

During the pandemic, an unusual number of thromboembolic complications have been described.[11] In our cohort, four patients were diagnosed with pulmonary embolism (PE) and one with arterial thrombosis (acrocyanosis of the limbs) after COVID-19 diagnosis, with a fatal outcome (4/5 died).

TABLE 1 Clinical features of the 41 COVID-19 patients with hematological malignancies

Patients characteristics	N = 41 (%)
Gender	
Male	22 (53)
Female	19 (47)
Median age (range), y	76 (37-92)
Hematologic malignancy	
Non-Hodgkin lymphoma	14 (36)
Chronic lymphocytic leukemia	9 (22)
Plasma cell dyscrasia	5 (12)
Acute leukemia	4 (10)
Myelodysplastic syndrome	4 (10)
Myeloproliferative neoplasm	4 (10)
Hodgkin lymphoma	1 (2.5)
Hematologic malignancy status	
Complete remission	13 (32)
Partial remission	6 (15)
Stable disease	11 (27)
Progressive disease	11 (27)
Treatment for hematologic malignancy	
Active	21 (51)
No treatment	5 (12)
Follow-up after treatment	15 (37)
Comorbidities	
Hypertension	22 (54)
Chronic obstructive pulmonary disease	10 (24)
Diabetes	9 (22)
Ischemic heart disease	6 (15)
Renal failure	6 (15)
Previous cancer	4 (10)
Atrial fibrillation	4 (10)
Previous venous thromboembolism	2 (5)
Co-existing hematological cancer	1 (2.5)
Asthma	1 (2.5)
Rheumatoid arthritis	1 (2.5)
Thromboembolic event	
Pulmonary embolism	4 (10)
Arterial thrombosis	1 (2.5)
No event	36 (8)
Signs and symptoms	
Fever	22 (54)
Cough	17 (41)
Shortness of breath	13 (32)
Malaise	11 (27)
Myalgia	6 (15)
Headache	5 (12)
Renal insufficiency	5 (12)
Diarrhea	5 (12)
Nausea	4 (10)
Chest pain	3 (7)
Expectoration	3 (7)
Disseminated intravascular coagulopathy	2 (5)
Seizures	1 (2.5)
Covid-19 treatment	
Hydroxychloroquine	36 (88)
Azithromycin	32 (78)
Lopinavir-Ritonavir	15 (37)
Methylprednisolone	14 (34)
Tocilizumab	9 (22)
Interferon	4 (10)
Immunoglobulins	2 (5)
Anakinra	1 (2.5)
No treatment	5 (12)

As of June 30, 2020, with a median follow-up of 51 days (range, 7-110) since the beginning of symptoms, 15/41 patients had died, with a CFR of 36.6%. Next, we compared our CFR with the same one of 1774 nonhematological COVID-19 patients admitted to the hospital during the same period. The percentage of deceased patients in the nonhematological cohort was 16.9% in contrast to 36.6% in the hematological individuals. The CRF in hematological patients with COVID-19 was almost three-fold compared to nonhematological patients (OR 2.83; CI 95% 1.48-5.41) as shown in Table 2. These results are in line with the bad outcome observed in previous reports.[4-9] However, these data need further validation due to the small simple size and the possible effect of confounding factors.

Moreover, we analyzed the relationship of clinical and laboratory findings with outcome. We observed that the severity of pneumonia was associated with increased risk of dying from COVID-19 in hematological patients (HR 3.76; CI 95% 1.48-9.54). In addition, patients with progressive disease had a significantly worse outcome than those in any other situation (HR 4.41; CI 95% 1.17-9.89). We failed to find a significant association with other characteristics (active treatment (HR 1.68 [95% CI 0.59-4.79]); ≥3 comorbidities (HR 2.22 [95% CI 0.79-6.18]); ≥80 years old (HR 1.92 [95% CI 0.69-5.32]); thromboembolic events (HR 2.14 [95% CI 0.68-6.76]). The relationship of mortality depending and the type of underlying malignancy (myeloid/lymphoid) is controversial,[7,8] however, we did not see differences in outcomes between these groups (HR 1.01; CI 95% 0.71-1.27).

We did not observe significant differences among laboratory findings and outcome either (Table 3). However, although without significance, median hemoglobin, lymphocyte count, and platelet count were lower in patients with fatal outcome, while median IL-6, ferritin, D-dimer, and LDH were higher, as previously described in patients with COVID-19.[11]

TABLE 2 Comparison of mortality between the global series and the hematological patients

	Global series			Onco-hematological				
Age	Alive	Death	% Death	Alive	Death	% Death	Odds Ratio (CI 95%)	*P*-value
All patients	1474	300	16.9	26	15	36.6	2.83 (1.48-5.41)	.002
0-60	652	25	3.7	7	2	22.2	7.45 (1.47-37.71)	.045
61-70	271	42	13.4	3	2	40	4.30 (0.69-26.51)	.14
71-80	279	71	20.3	10	5	33.3	1.96 (0.65-5.93)	.18
>80	272	162	37.3	6	6	50	1.68 (0.53-5.30)	.27

TABLE 3 Laboratory findings at COVID-19 diagnosis depending on outcome

Parameter (median)	Recovered patients	Deceased patients	*P*-value
Hemoglobin (g/dL)	11.9 (4.6-15.9)	10.5 (6.6-15.2)	.095
Neutrophil count ($\times 10^9$/L)	4.6 (0.1-25.7)	4.7 (0.0-34.1)	.723
Lymphocyte count ($\times 10^9$/L)	0.9 (0.3-7.8)	0.7 (0.3-175.8)	.746
Platelet count ($\times 10^9$/L)	212 (16-630)	165 (3-376)	.137
IL-6 level, pg/mL	13.6 (5.5-378)	41.3 (36.3-54.5)	.700
Ferritin level, mg/L	380 (151-610)	1309.5 (831-1788)	.333
D-dimer level, ng/mL	1050 (490-14.400)	2360 (490-14.400)	.63
LDH, U/L	232 (94-413)	326 (164-1391)	.05
CRP (mg/L)	100 (2-1203)	124 (4-348)	.457

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase.

In the 26 surviving patients, median duration of viral shedding was 32.7 days (range 10-70). In general, population median time to PCR negativity is around 20 days[9] in survivors, suggesting our data a role of the immunocompromised system in the delay of the virus clearance. Interestingly, one acute myeloid leukemia patient under induction therapy at the time of COVID-19 maintains a positive PCR after 70 days of follow-up. This report confirms a longer viral shedding in hematological patients as recently described.[9] Although the significance of a positive PCR is controversial in the absence of COVID-19 symptoms, it provides key information in onco-hematological patients as it helps to guide treatment decisions such as chemotherapy, HSCT programming, or CAR-T therapy.

Our study has several limitations like its small sample size and its retrospective nature. Moreover, the number of hematological patients with COVID-19 could be underestimated because several patients did not consult with the hospital, and there is a lack of data on patients who developed COVID-19 in the community and were not tested. Registry and multicentric studies are required to better describe the impact of COVID-19 in our patients, but still case series reports are important due to the great impact of COVID-19 on worldwide healthcare system and the high mortality rates described in short periods.

The CFR of 36.6% and the high prevalence of nosocomial origin of COVID-19 described in our series support the strategies proposed by different guidelines that recommend adapting clinical practice[12] in order to reduce access to the hospital in those patients with controlled disease. These recommendations should be accomplished not only during the peak of the pandemic, but also in the long term, as it will be crucial to protect our patients against COVID-19 dreadful effects.

Our study highlights the following conclusions: First, we have shown that hematological malignancies might be a poor prognostic factor for COVID-19, especially in the presence of progressive disease; second, we have observed that in hematological patients, the risk of nosocomial infection of COVID-19 is high. Finally, blood cancer patients show a longer viral shedding, possibly because of their disrupted immune system. To sum up, our data suggest the need for strong proactive strategies to reduce likelihood of infection and improve early identification in this vulnerable patient population.

KEYWORDS

COVID-19, hematological malignancies, infection, mortality rate, SARS-CoV-2 RT-PCR

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHORS CONTRIBUTION

MSA and IGGyM designed the study, analyzed the data, and wrote the paper. MSI, IGGyM, CMN, JCh, EL, MF, KM, and JAHR provided patient care samples and clinical data. PR managed institution general database. JAHR conceived the study, supervised the research, and critically reviewed the manuscript. All authors discussed the results and revised the manuscript.

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