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Case Reports and Series

Higher mortality of hospitalized haematologic patients with COVID-19 compared to non-haematologic is driven by thrombotic complications and development of ARDS: An age-matched cohorts study☆

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ABSTRACT

Background and Objectives: The characteristics of COVID-19 in haematologic patients compared to non-haematologic patients have seldom been analyzed. Our aim was to analyze whether there are differences in clinical characteristics and outcome of haematologic patients with COVID-19 as compared to non-haematologic.
Patients and methods: Retrospective cohort study in 2 University hospitals of patients admitted with laboratory-confirmed COVID-19 included in the SEMICOVID19 database. The cohort with underlying haematologic disease was compared to a cohort of age and date-of-COVID-19-matched controls without haematologic disease (1:2).
Results: 71 cases and 142 controls were included from March-May 2020.
Twenty (28.1%) had received recent chemotherapy. Twelve (16.9%) were stem cell transplant recipients (SCT). Eleven (15.5%) were neutropenic concurrently with COVID-19 diagnosis.
Haematologic patients presented ARDS (58.5 vs 20.7%, p = 0.0001), thrombotic complications (15.7 vs 2.1%, p = 0.002), DIC (5.7 vs 0.0%, p = 0.011), heart failure (14.3 vs 4.9%, p = 0.029) and required ICU admission (15.5 vs 2.8%, p = 0.001), MV (14.1% vs 2.1%, p 0.001), steroid (64.8 vs 33.1%, p = 0.0001), tocilizumab (33.8 vs 8.5%, p = 0.0001) or anakinra treatment (9.9% vs 0%, p = 0.0001) more often. In-hospital mortality was significantly higher (38.0% vs 18.3%, p = 0.002).
Conclusions: Our results suggest COVID-19 has worse outcomes in haematologic patients than in non-haematologic, independently of age, and that the development of ARDS and thrombotic complications drive the higher in-hospital mortality.

Abbreviations: ARDS, acute respiratory distress syndrome; C-RP, C-reactive protein; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID-19, Coronavirus disease 2019; DIC, disseminated intravascular coagulation; ECOG scale, Eastern Cooperative Oncology Group scale; G-CSF, granulocyte stimulating factor; HFNC, high flow nasal cannula; ICU, Intensive Care Unit; IL6, Interleukin 6; IQR, interquartile range; LDH, Lactate dehydrogenase; MDS, myelodysplastic syndrome; MM, multiple myeloma; MV, mechanical ventilation; NHL, non-Hodgkin lymphoma; NIMV, non-invasive mechanical ventilation; OR, Odds ratio; PaO2/FiO2, arterial oxygen tension/inspiratory oxygen fraction; PEEP, positive end expiratory pressure; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SCT, stem cell transplantation; SD, standard deviation.

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Introduction

Haematologic patients present a high risk for infection, due to immune-compromise secondary to underlying disease and subsequent therapy. Viral infections such as RSV or Influenza that are considered mild in immunocompetent hosts can become life-threatening in certain haematologic patients (Kmeid et al., 2016; Sheshadri et al., 2019).

The characteristics of SARS-CoV-2 infection and COVID-19 in haematologic patients are not yet well known. In the context of COVID-19 pandemic, the underlying haematologic disease could influence the inflammatory response and viral clearance, and modify manifestations and outcome of the disease (Chamilos et al., 2021).

Studies published so far suggest haematologic patients with COVID-19 present a higher mortality as compared with general population data (García-Suárez et al., 2020). However, the characteristics of COVID-19 in haematologic patients as directly compared to non-haematologic patients have seldom been analyzed. There is a lack of information regarding differences in clinical presentation, incidence of different complications and management of patients with haematologic malignancy and COVID-19, compared to non-haematologic cases. The scarce prior published series that compare to the general population (Passamonti et al., 2020) present mainly population-based data and lack detailed information of cases.

We present a cohort of haematologic patients with COVID-19, and compare them to non-haematologic patients with COVID-19.

Material/Patients and methods

Setting and study design

We performed a retrospective cohort study in 2 University hospitals in Madrid, Spain, of admitted patients with SARS-CoV-2 laboratory-confirmed pneumonia included in the SEMICOVID19 Registry (compiled by the Spanish Society of Internal Medicine) from March to May 2020. Both centres are tertiary teaching hospitals, with reference Haematology Departments, that possess stem cell transplantation units and treat complex Haematology patients.

The SEMICOVID19 is an ongoing, nationwide multicentre anonymized online database of consecutive adult patients admitted with SARS-CoV-2 laboratory-confirmed pneumonia from 131 different Spanish hospitals. Inclusion criteria for the registry were age $\geq$ 18 years and first hospital discharge with a confirmed diagnosis of COVID-19; exclusion criteria were subsequent admissions of the same patient and denial or withdrawal of informed consent, as described elsewhere (Casas-Rojo et al., 2020). Patients were cared for according to local protocols and clinical judgment of their attending physician.

For the present study, only 2 of these hospitals were selected that had included all their haematologic hospitalized patients with COVID-19 in the Registry database. A retrospective cohort study was designed to compare the differences between patients with underlying haematologic disease and patients without underlying haematologic disease. All patients with underlying haematological disease were selected and two controls without haematologic disease were selected for each haematologic patient, matched by age and date of COVID-19. To ensure a standard process of choosing controls, an algorithm was used to select those of the same age among the possible controls diagnosed at the nearest date of COVID diagnosis.

Data collection

The SEMICOVID Registry includes epidemiological, clinical, laboratory and radiologic data extracted from electronic medical records. For more comprehensive information on the registry, see previously published works (Casas-Rojo et al., 2020).

A complementary standardized form was fulfilled for haematologic patients that included specific data about haematologic disease: underlying haematologic disease, ECOG, status, therapy, stem cell transplantation.

Definitions

We considered SARS-CoV-2 infected patients those with a microbiological confirmation by reverse transcription polymerase chain reaction (RT-PCR) testing of a respiratory sample. All patients admitted with symptomatic COVID-19 infection were included, with or without pneumonia.

We included in the "Haematologic disease cohort" patients (or "Haematologic patients") admitted with SARS-CoV-2 infection who had an underlying active haematological malignancy, or were stem cell-transplantation (SCT) recipients (as treatment for haematological malignancy). Patients were considered as having active onco-hematologic disease when they were under treatment (chemotherapy, or targeted therapy) or being still immunocompromised due to their underlying hematological condition or treatment. The "Non-haematologic disease cohort" (or "Non-haematologic patients") included patients admitted with SARS-CoV-2 infection and without onco-haematologic disease or SCT. Patients with active solid tumours were excluded from both cohorts and will be analysed separately.

Disease status at the time of SARS-CoV-2 detection was defined according to each specific disease's revised criteria for leukemia, myeloproliferative neoplasm, multiple myeloma and lymphoma (Döhner et al., 2017; Cheson et al., 2014; Kumar et al., 2016).

Performance status at the diagnosis of COVID-19 was graded according to the Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982).

The diagnosis and grading of ARDS was determined according to modified Berlin criteria (Force et al., 2012) (in non-ventilated patients, the PEEP value in the modified criteria was not taken into consideration): Mild: PaO2/FiO2 200–300 mmHg (PEEP or CPAP $\geq$ 5 cmH2O, or non-ventilated); Moderate: PaO2/FiO2 100–200 (PEEP $\geq$ 5 cmH2O, or non-ventilated); Severe: PaO2/FiO2 $\leq$ 100 mmHg (PEEP $\geq$ 5 cmH2O, or non-ventilated).

The main outcome variable was in-hospital mortality.

Statistical analysis

Quantitative variables were expressed as means and standard deviations (SD) and/or medians and interquartile ranges, and qualitative variables as frequencies and percentages.

To compare differences between haematologic and non-haematologic cohorts, the Mann-Whitney *U* test, $\chi 2$ test, Fisher's exact test or Student *t* test were used where appropriate.

To explore risk factors associated with in-hospital death among haematologic patients, univariable and multivariable logistic regression models were used. Variables with a $p < 0.05$ in univariable analyses were selected into the multivariable.

All statistical analyses were performed using SPSS system (version 26.0 for Windows, SPSS Inc., Chicago, IL, USA). The statistical significance level was set at a two-sided p value of < 0.05. An odds ratio (OR) was reported along with 95% confidence interval (CI).

Results

From March to May 2020, 5592 patients with COVID-19 were admitted to the 2 hospitals. Among them, 71 (1.3%) cases had an underlying haematologic disease. One-hundred and forty-two patients with COVID-19 but without haematologic disease admitted to the hospital during the study period were selected as the control cohort.

Patients were followed until discharge, and if readmitted, until subsequent discharge (median follow-up of 7 days (IQR 4–14)).

Characteristics of underlying haematologic disease

Characteristics of haematologic diseases are summarized in Table 1 and Fig. 1. The most common was NHL, followed by MM, CLL and MDS. In 14.1% the haematologic disease was at an initial stage, whereas in 16.9% it was refractory or relapsed. Performance status measured by ECOG scale was > 1 in 12.9 %.

Twelve patients (16.9%) were stem cell transplantation recipients (SCT). In the majority of cases SCT was autologous (58.3% autologous versus 41.7% allogenic). Median time from SCT to COVID-19 diagnosis was 607 days (IQR 259–1291 days).

Forty-five cases (63.4%) were under oncologic therapy at COVID-19 diagnosis, which in 25 (55.6%) of cases was considered as palliative/ symptomatic care.

Twenty patients (28.1%) had received chemotherapy in the prior month and 11 (15.5%) were neutropenic concurrently with COVID-19 diagnosis. Among these, 6 (54.5%, 8.5% of the whole series) received G-CSF. In seven cases (33.3%) chemotherapy was administered in combination with targeted therapy.

Thirty-two patients (45%) were receiving targeted therapy, including 15 (21.1%) under rituximab, 10 (14.1%) treated with ibrutinib (7) or other BTK inhibitors (3), 6 (8.5%) with bortezomib (4) or other proteasome inhibitors (2), 2 with imatinib, 2 with obinutuzumab (one of them combined with zanabrutinib) and 1 with ofatumumab (combined with ibrutinib), 1 with darutumumab (combined with carfilzomib) and 1 with ruxolitinib. Treatment with ibrutinib or other BTK inhibitors was maintained throughout the COVID episode in all cases.

Comparison of haematologic and non-haematologic patients with COVID-19

Differential characteristics of patients with and without haematologic disease are shown in Table 2 (baseline characteristics) and Table 3 (management and outcome characteristics).

Baseline significant differences included a higher age-adjusted Charlson comorbidity index (5.4 vs 3.4, p = 0.0001), creatinine (1.26 vs 0.95 mg/dl, p = 0.027), C-reactive protein (111 vs 79 mg/dl, p = 0.023) and D-dimer levels (2893 vs 1077 ng/mL, p = 0.047), increased prevalence of neutropenia (15.5% vs 1.4%, p = 0.0001) and anemia (hemoglobin 11.9 vs 14.2 g/dl, p = 0.0001) and more frequent receipt of prior anticoagulants (21.1% vs 7.7 %, p = 0.003) and prior steroids (18.3% vs 3.5%, p = 0.024) or immunosuppressive therapy (26.7% vs 2.1%, p = 0.0001) in haematologic patients. Both cohorts had similar median age (70.7 vs 69.6 y, p = 0.734). Of note, there were no differences either in prevalence of baseline lymphopenia, thrombocytopenia or other alteration of coagulation parameters (different from D-dimer) between haematologic cases and controls, or in LDH, ferritin or IL6 levels.

Table 1
Underlying haematologic malignancy.

Patients with underlying hematologic disease	n = 71
Type of hematological malignancy	
Hodgkin lymphoma	1 (1.4%)
Non-Hodgkin lymphoma	21 (29.6%)
Chronic lymphocytic leukemia	13 (18.3%)
Acute lymphoblastic leukemia	1 (1.4%)
Acute myeloid leukemia	3 (4.2%)
Multiple myeloma	15 (21.1%)
Myelodysplastic syndrome	10 (14.1%)
Myeloproliferative neoplasm	6 (8.5%)
Rosai-Dorfman disease	1 (1.4%)
Hematological malignancy status	
Initial diagnosis	10 (14.1%)
Stable, no remission	16 (22.5%)
Relapsed or refractory	12 (16.9%)
Complete/partial response	33 (46.5%)
ECOG > 1	9 (12.9%)
Oncologic treatment	45 (63.4%)
Curative	20 (44.4%)
Palliative	25 (55.6%)
G-CSF treatment	6 (8.5%)
Stem cell transplant type	
Allogeneic	5 (7%)
Autologous	7 (9.9%)

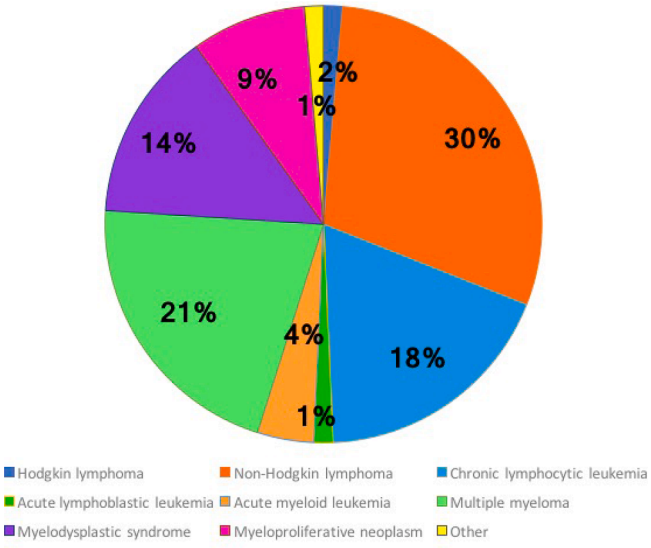

Fig. 1. Type of haematological malignancy.

Regarding outcome, haematologic patients presented ARDS (58.5 vs 20.7%, p = 0.0001), thrombotic complications (15.7 vs 2.1%, p = 0.002), disseminated intravascular coagulation (5.7 vs 0.0%, p = 0.011) and heart failure (14.3 vs 4.9%, p = 0.029) more often and required ICU admission (15.5 vs 2.8%, p = 0.001), mechanical ventilation (14.1% vs 2.1%, p 0.001), and steroid (64.8 vs 33.1%, p = 0.0001), tocilizumab (33.8 vs 8.5%, p = 0.0001) or anakinra treatment (9.9% vs 0%, p = 0.0001) in a higher proportion than controls. Length of stay after COVID-19 diagnosis was longer for haematologic patients (18 days (SD17.1) versus 7 (7.4) days, p 0.0001). Interestingly, haematologic patients did not present more infectious complications than non-haematologic. In 67 (31.5%) cases that had a follow-up SARS-CoV-2 PCR, there was a non-significant trend to a longer duration of positivity in haematologic patients (11 vs 4.5 days, p = 0.861).

In-hospital mortality was significantly higher among haematologic cases versus controls (38.0% vs 18.3%, p = 0.002). However, there were no significant differences in in-hospital mortality in patients who developed ARDS, or required ICU admission or ventilation, according to the presence of haematologic disease (Table 3).

Risk factors for in-hospital mortality among haematologic patients

Univariable analysis of factors associated with in-hospital mortality are displayed in Table 4.

When considering only haematologic patients, only development of ARDS (96.3 vs 36.4, p 0.0001) (OR 37.635 (4.583–309.060) p 0.001) was independently associated with a higher probability of in-hospital death in the multivariable analysis. Other factors such as recent chemotherapy, neutropenia, targeted therapies or uncontrolled haematologic disease were not predictors of in-hospital mortality in the multivariable analysis.

In-hospital mortality in recipients of SCT was similar to that of non-recipients (33.3% vs 39% (p = 0.999), however, there were no pre-engraftment cases of SCT.

Administration of G-CSF in haematologic patients was not associated with development of ARDS (p = 0.417).

Table 2
Baseline characteristics.

Demographic and Clinical Characteristics (n, %)	Haematological malignancy (71)	Non Haematological malignancy (142)	p
Demographic Characteristics			
Sex			0.378
Male	44 (61.9%)	77 (54.2%)	
Female	27 (38.0%)	64 (45.1%)	
Age			
(median-IQR)	70.7 (59.6–80.7)	69.6 (59.5–80.3)	0.734
(mean-SD)	68.6 (13.9)	68.4 (13.8)	0.915
Age-adjusted Charlson comorbidity index (mean-SD)	5.4 (2.6)	3.4 (2.4)	0.0001
Ethnicity			0.983
Caucasian	63 (88.7%)	124 (87.3%)	
Latin American	6 (8.5%)	13 (9.2%)	
Other	1 (1.4%)	2 (1.4%)	
COVID-19 close contact			0.088
No	58 (81.7%)	96 (67.6%)	
Yes	12 (17.1%)	39 (27.5%)	
Acquisition			0.174
Community-acquired	59 (83.1%)	129 (90.8%)	
Hospital-acquired	7 (9.9%)	6 (4.2%)	
Nursing home	5 (7.0%)	6 (4.2%)	
Comorbidities and prior therapies			
Enolism	2 (2.8%)	5 (3.5%)	0.999
Smoking status			0.133
No	45 (63.4%)	106 (74.6%)	
Ex-smoker	22 (31%)	27 (19%)	
Smoker	3 (4.2%)	4 (2.8%)	
Hypertension			0.246
Yes	35 (42.3%)	58 (40.8%)	
ACE inhibitors	11 (31.4%)	18 (31%)	0.673
ARBs	14 (40%)	29 (50%)	0.999
Dyslipidemia			0.223
Yes	29 (40.8%)	45 (31.7%)	
Statins	26 (89.7%)	43 (30.3%)	0.356
Atrial fibrillation	11 (15.5%)	11 (7.7%)	0.097
Obesity (Body Mass Index > 30)	14 (19.7%)	33 (23.2%)	0.721
Degenerative neurological disease	3 (4.2%)	11 (7.7%)	0.394
Chronic kidney disease			0.131
Moderate/Severe	7 (9.9%)	6 (4.2%)	
Dialysis			0.346
Hemodialysis	2 (2.8%)	3 (2.1%)	
Peritoneal dyalisis	1 (1.4%)	0 (0.0%)	
Solid-organ			0.687
transplantation	1(1.4%)	1 (0.7%)	
Liver	0 (0.0%)	1 (0.7%)	
Kidney			
Immunosuppression			**0.0001**
Azathioprine	0 (0.0%)	1 (0.7%)	
Methotrexate	0 (0.0%)	1 (0.7%)	
Cyclophosphamide	0 (0.0%)	2 (1.4%)	
Others	17 (24%)	1 (0.7%)	
Diabetes mellitus without	11 (15.5%)	23 (16.2%)	0.999
end-organ damage	6 (8.5%)	6 (4.2%)	0.220
Diabetes mellitus with	13 (18.3%)	25 (17.6%)	0.851
end-organ damage	5 (7%)	13 (9.2%)	0.795
Metformin	2 (2.8%)	0 (0.0%)	0.110
DPP-4 inhibitors	3 (4.2%)	5 (3.5%)	0.999
GLP-1 agonists	5 (7%)	5 (3.5%)	0.307
SGLT2 inhibitors			
Insulin			
Prior systemic corticosteroids	13 (18.3%)	5 (3.5%)	**0.001**
Hydroxychloroquine	1 (1.4%)	0 (0.0%)	0.335
Biological agents	7 (9.9%)	2 (1.4%)	**0.007**
Anticoagulants			**0.003**
VKAs	6 (8.5%)	3 (2.1%)	
DOACs	5 (7.0%)	8 (5.6%)	
LMWH	4 (5.6%)	0 (0.0%)	
	8 (11.3%)	6 (4.2%)	0.075
Acute myocardial infarction			
Angina	6 (8.5%)	7 (4.9%)	0.366
Acetylsalicylic acid	19 (26.8%)	25 (17.6%)	0.151
Heart failure	6 (8.5%)	8 (5.6%)	0.559
Chronic obstructive pulmonary disease	1 (1.4%)	9 (6.3%)	0.170
Asthma	3 (4.2%)	12 (8.5%)	0.395
Inhaled steroids	3 (4.2%)	10 (7.0%)	0.430
Cerebrovacular disease	2 (2.8%)	4 (2.8%)	0.999
Dementia	2 (2.8%)	11 (7.7%)	0.227
Peripheral vascular disease	1 (1.4%)	4 (2.8%)	0.667
Liver disease			
Mild	1 (1.4%)	8 (5.6%)	0.277
Moderate/Severe	1 (1.4%)	2 (1.4%)	0.999
Connective tissue disease	1 (1.4%)	4 (2.8%)	0.667
Gastroduodenal ulcer	1 (1.4%)	3 (2.1%)	0.999
HIV	1 (1.4%)	1 (0.7%)	0.999
Obstructive sleep apnea	5 (7.0%)	0 (0.0%)	0.536
Clinical findings at admission			
Cough			0.682
Dry	37 (52.1%)	82 (57.7%)	
Expectoration	14 (19.7%)	29 (20.4%)	
Arthromyalgia	15 (21.1%)	50 (35.2%)	**0.040**
Ageusia	1 (1.4%)	8 (5.6%)	0.277
Anosmia	2 (2.8%)	8 (5.6%)	0.503
Asthenia	37 (52.1%)	62 (43.7%)	0.381
Anorexia	14 (19.7%)	14 (9,9%)	0.057
Pharyngeal ache	11 (15.5%)	14 (9,9%)	0.264
Headache	9 (12.7%)	15 (10.6%)	0.652
Low grade fever	15 (21.1%)	24 (16.9%)	0.525
Fever	44 (62.0%)	99 (69.7%)	
Dyspnea	28 (39.4%)	81 (57.0%)	**0.020**
Diarrhea	14 (19.7%)	21 (14.8%)	0.433
Nausea	7 (9.9%)	15 (10.6%)	0.999
Vomit	3 (4.2%)	9 (6.3%)	0.755
Abdominal pain	4 (5.6%)	10 (7.0%)	0.778
Confusion	5 (7.0%)	13 (9.2%)	0.795
Tachypnea	17 (23.9%)	47 (33.1%)	0.201
Lung auscultation			
Crackling	44 (62%)	76 (53.5%)	0.362
Wheezing	0 (0.0%)	8 (5.6%)	0.053
Ronchi	2 (2.8%)	10 (7.0%)	0.345
Laboratory and radiology parameters			
Positive PCR sample			0.363
Nasopharyngeal	65 (91.5%)	133 (93.7%)	
Sputum	4 (5.6%)	8 (5.6%)	
Broncho-alveolar lavage	1 (1.4%)	0 (0.0%)	
Neutropenia			
Neutrophils < 500 (cells/μL)	5 (7.0%)	1 (0.7%)	**0.009**
Neutrophils < 1000 (cells/μL)	11 (15.5%)	2 (1.4%)	**0.000**
Blood cell counts (cells/μL) (mean-SD)			
Absolute white blood cell count	10,245 (14006)	7827 (8733)	0.187
Absolute lymphocyte count	4001 (9880)	1583 (5443)	0.058
Absolute neutrophil count	4509 (3750)	4948 (2361)	0.370
Hemoglobin (mean-SD)	11.9 (2.5)	14.2 (1.7)	**0.0001**
C-RP (mg/L) (mean-SD)	111 (105)	79 (79)	**0.023**
Serum creatinine (mg/dL) (mean-SD)	1.26 (1.07)	0.95 (0.62)	**0.027**
LDH (U/L) (mean-SD)	461 (665)	327 (126)	0.110
Serum ferritin (μ/L) (mean-SD)	1280 (1708)	1217 (1768)	0.875
IL-6 (pg/mL) (mean-SD)	184 (291)	79 (121)	0.152
D-dimer (ng/mL) (mean-SD)	2893 (6431)	1077 (1376)	**0.047**

(*continued on next page*)

Table 2 (*continued*)

Demographic and Clinical Characteristics (n, %)	Haematological malignancy (71)	Non Haematological malignancy (142)	p
Alveolar infiltrates			0.805
Unilateral	10 (14.1%)	26 (18.3%)	
Bilateral	27 (38.0%)	53 (37.3%)	
Ground-glass infiltrates			**0.016**
Unilateral	4 (5.6%)	16 (11.3%)	
Bilateral	36 (50.7%)	89 (62.7%)	
Pleural effusion			**0.019**
Unilateral	3 (4.2%)	1 (0.7%)	
Bilateral	5 (7.0%)	2 (1.4%)	
Influenza PCR test			**0.029**
Negative	6 (8.5%)	25 (17.6%)	
Positive	2 (2.8%)	0 (0.0%)	
Not performed	62 (87.3%)	112 (78.9%)	
Urinary antigens			0.114
Negative	19 (26.8%)	56 (39.4%)	
S. pneumoniae	1 (1.4%)	2 (1.4%)	
Not performed	49 (69%)	74 (52.1%)	

Discussion

Our results show that, despite immunosuppression, haematologic patients with COVID-19 present significantly more respiratory and thrombotic complications as compared to non-haematologic patients, and a higher in-hospital mortality.

Some of the cancer-associated factors that have been advocated to contribute to worse outcomes of SARS-CoV-2 infection (lymphopenia and lymphocyte dysfunction, hypercoagulability, immuno-metabolic deregulation related to myeloid cell dysfunction) converge in patients with haematological malignancy. On the other hand, chemotherapy-induced neutropenia and monocytopenia might attenuate the hyper-inflammatory response to the virus, whereas neutrophil recovery, treatment with G-CSF or immunotherapy could enhance it (Chamilos et al., 2021).

Several series attribute the increased mortality of haematologic patients to their higher age (García-Suárez et al., 2020). Age is an important prognostic factor in COVID-19 (Moreno-Torres et al., 2021). However, in our age-matched cohort, we still observed a significant difference in mortality between haematologic and non-haematologic cohorts. Nevertheless, patients with ARDS and patients requiring ICU had a similar mortality, regardless of the presence underlying haematologic disease. In the present series, both the development of ARDS and thrombotic complications were more frequent and could account for the increased mortality, in the haematologic cohort.

In COVID-19 patients, ARDS is driven by the inflammatory response to SARS-CoV-2, rather than by direct viral damage (Osuchowski et al., 2021). However, despite immunosuppression, haematologic patients in this series presented ARDS more often than non-haematologic. Haematologic patients with pneumonia are at risk of developing ARDS during neutropenia recovery (Rhee et al., 2009; Malek et al., 2021). It is a matter of controversy whether G-CSF could exacerbate the effect of neutrophil recovery contributing to ARDS (Rhee et al., 2009; Mignard et al., 2019). G-CSF upregulates the production of cytokines that increase alveolar permeability and neutrophil influx, and may enhance secretion of pro-inflammatory cytokines by alveolar macrophages (Rhee et al., 2009). In the present series, G-CSF was not a risk factor for ARDS, although it was administered to only a minority of patients.

Nevertheless, endothelitis and coagulopathy leading to in-situ thrombosis is increasingly gaining consideration in the pathogenesis of respiratory failure in COVID-19 (Bonaventura et al., 2021). Microthrombosis seems to be involved in the physiopathology of acute respiratory distress syndrome (ARDS) (Bonaventura et al., 2021; O'Donnell et al., 2021). The development of a pro-thrombotic state is an important feature of COVID-19. In the present series, thrombotic events were strikingly more frequent in haematologic patients. Cancer is a well-known risk factor for thrombosis and, in particular, patients with

Table 3
Management and outcome.

Complications and outcome	Haematological malignancy (71)	Non Haematological malignancy (142)	p
COMPLICATIONS (n, %)			
Heart failure	10 (14.3%)	7 (4.9%)	**0.029**
Cardiac arrhythmia			0.116
Atrial cardiac arrhythmia	2 (2.8%)	3 (2.1%)	
Ventricular cardiac arrhythmia	2 (2.8%)	0 (0.0%)	
Acute myocardial infarction	2 (2.8%)	0 (0.0%)	0.108
Myocarditis	3 (4.2%)	0 (0.0%)	**0.035**
Stroke			0.283
Ischemic stroke	0 (0.0%)	1 (0.7%)	
Hemorrhagic stroke	1 (1.4%)	0 (0.0%)	
Acute kidney failure	15 (21.1%)	19 (13.4%)	0.164
Sepsis	4 (5.7%)	2 (1.4%)	0.094
Bacterial pneumonia	3 (4.2%)	12 (8.5%)	0.395
Persistance of positive SARS-CoV-2 PCR (in 67 cases with available control PCR)			
(mean-SD)	16.8 (18.3)	10.1 (13.8)	0.303
(median-IQR)	11 (0.0–26.5)	4.5 (0.0–16.5)	0.861
Disseminated intravascular coagulation (DIC)	4 (5.7%)	0 (0.0%)	**0.011**
Thromboembolic disease	11 (15.5%)	3 (2.1%)	**0.002**
Deep vein thrombosis (DVT)	2 (2.8%)	1 (0.7%)	
Pulmonary thromboembolism (PE)	8 (11.3%)	2 (1.4%)	
DVT + PE	1 (1.4%)	0 (0.0%)	
Acute peripheral arterial disease	1 (1.4%)	1 (0.7%)	0.552
Acute respiratory distress syndrome (ARDS)	41 (58.5%)	29 (20.7%)	**0.0001**
Mild ARDS	6 (8.5%)	9 (6.3%)	
Moderate ARDS	10 (14.1%)	3 (2.1%)	
Severe ARDS	25 (35.3%)	17 (12%)	
Shock	3 (4.2%)	2 (1.4%)	0.335
Multiorgan failure	4 (5.6%)	4 (5.6%)	0.444
MANAGEMENT			
Systemic corticosteroids	46 (64.8%)	47 (33.1%)	**0.0001**
Systemic corticosteroids maximum daily dose (mg prednisone or equivalent) (mean-SD)	220 (214)	104 (70)	**0.001**
Days of treatment with systemic corticosteroids (mean-SD)	11.3 (9.6)	5.6 (5.6)	**0.001**
Cumulative dose of systemic corticosteroids during admission (mean-SD)	997 (1015)	319 (214)	**0.002**
Number of days with systemic corticosteroid pulses (>150 mg prednisone equivalent) (mean-SD)	2 (2.3)	0.5 (1.0)	**0.000**
Lopinavir/ritonavir	40 (56.3%)	94 (66.2%)	0.177
Beta Interferon	9 (12.7%)	34 (24%)	0.070
Remdesivir	1 (1.4%)	0 (0.0%)	0.340
Hydroxichloroquine	63 (44.4%)	135 (95.1%)	0.097
Colchicine	0 (0.0%)	1 (0.7%)	0.999
Tocilizumab	24 (33.8%)	12 (8.5%)	**0.0001**
Inmunoglobulins	1 (1.4%)	0 (0.0%)	0.330
Anakinra	7 (9.9%)	0 (0.0%)	**0.0001**
Baricitinib	0 (0.0%)	0 (0.0%)	NA
Intensive care unit (ICU) admission	11 (15.5%)	4 (2.8%)	**0.001**
Ventilation			
High flow nasal cannula	14 (19.7%)	19 (13.4%)	0.232
Non-invasive mechanical ventilation (NIMV)	7 (9.9%)	13 (9.2%)	0.999
Invasive mechanical ventilation (IMV)	10 (14.1%)	3 (2.1%)	**0.001**
Prone positioning therapy	12 (17%)	8 (5.6%)	**0.012**

(*continued on next page*)

Table 3 (*continued*)

Complications and outcome	Haematological malignancy (71)	Non Haematological malignancy (142)	p
Hospital mortality (overall)	27 (39%)	26 (18.3%)	**0.002**
-in patients who developed ARDS	24 (64.9%)	16 (57.1%)	0.610
-in patients who required ICU admission	7 (63.6%)	2 (50%)	0.999
-in patients who required MV	6 (60%)	1 (33.3%)	0.559
-in patients who required NIMV	5 (71.4%)	9 (69.2%)	0.999
Outcome			
Death during admission or readmission	30 (42.3%)	26 (18.3%)	**0.002**
Length of stay after COVID diagnosis (mean-SD)	18 (17.1)	7 (7.4)	**0.0001**
Re-admission	7 (9.9%)	5 (3.5%)	0.110
Reason for discharge			**0.0001**
Improvement: Home	39 (55%)	114 (89.3%)	
Convalescence: support centre	5 (7%)	2 (1.4%)	
Death	27 (38%)	26 (18.3%)	

active onco-haematologic conditions are known to be at higher risk for thromboembolism (Kekre and Connors, 2019). The baseline predisposition for thrombotic events seems to place haematologic patients more at risk for developing COVID-19 complications, both at the macro and at the microvascular level.

In immune-compromised patients there is a trend to longer persistence of viral shedding (Taramasso et al., 2021) that could contribute to a greater direct damage and mortality. Persistence of positive PCR could not be adequately evaluated in this retrospective series, as only 35% of cases had at least one control test after the diagnosis of COVID. Among those, there was a non-significant trend to a longer persistence of SARS-CoV-2 positivity.

Several studies report an inferior mortality of stem cell transplantation recipients as compared to other haematologic patients (Piñana et al., 2020). In published series, median time from SCT was, in general, long, and patients had had time enough to recover before presenting COVID-19. In addition, therapies typically used for graft versus host disease could mitigate the inflammatory response (Saraceni et al., 2021). On the contrary, outcome of recently transplanted patients that suffer from SARS-CoV-2 infection during the pre-engraftment period is not well known, and cases of ARDS at the moment of neutrophil recovery have been described (Malek et al., 2021). In our series, median time from transplantation to COVID-19 was close to 2 years and no pre-engraftment cases were detected. Nevertheless, we were not able to find differences in in-hospital mortality as compared to non-transplant recipients.

Patients receiving small molecule kinase inhibitors (such as JAK or BTK inhibitors) might be protected from hyper-inflammation, and it has been speculated that discontinuation of such therapies in cancer patients with COVID-19 could unleash the hyper-inflammatory response to SARS-CoV-2, in addition of adversely affecting the outcome of the underlying malignancy (Wijaya et al., 2021; Stack et al., 2021). In our series, all patients who were under ibrutinib or other BTK inhibitors maintained it throughout the COVID-19 episode. There were no significant differences in outcome according to BTK inhibitor treatment, though the sample is too small to draw any conclusion.

The major strength of the present study is the direct comparison of a cohort of haematologic patients with COVID-19 with a non-haematologic cohort matched by age and date of diagnosis of COVID. This allows to avoid bias secondary to different age range of patients with haematologic disease, and bias secondary to presentation in different moments of the COVID-19 learning curve at the beginning of the pandemic. Patients included were only those admitted to two reference hospitals in Madrid, which ensures the homogeneity in management and therapeutic options, and increases the probability of the observed differences being attributable to differences in the response to SARS-CoV-2 in haematologic patients.

Limitations of our study include the small simple size and the

Table 4
In-hospital mortality in patients with haematologic disease and COVID-19.

Haematologic patients mortality (n, %)	Non-survivors (27)	Survivors (44)	p
Age (mean, SD)	72.5 (16.4)	66.2 (11.6)	0.065
Sex			0.318
Male	19 (70.4%)	25 (56.8%)	
Female	8 (29.6%)	19 (43.2%)	
Race			0.694
Caucasian	25 (92.6%)	38 (86.4%)	
Latin	2 (7.4%)	4 (9.1%)	
Haematological malignancy status			0.278
Initial diagnosis	5 (18.5%)	5 (11.4%)	
Stable, no remission	5 (18.5%)	11 (25.0%)	
Relapsed or refractory	7 (25.9%)	5 (11.4%)	
Complete/partial response	10 (37.0%)	23 (52.3%)	
ECOG > 1	7 (26.9%)	2 (4.5%)	**0.011**
Oncologic treatment			0.372
Curative	6 (22.2%)	14 (31.8%)	
Palliative	11 (40.7%)	14 (31.8%)	
Chemotherapy during the last month	7 (25.9%)	13 (29.5%)	0.563
Rituximab	8 (29.6%)	7 (15.9%)	0.232
Ibrutinib	2 (7.4%)	5 (11.4%)	0.701
G-CSF	2 (7.4%)	4 (9.1%)	0.999
Stem cell transplant recipient	4 (14.8%)	8 (18.2%)	0.999
Allogeneic	2 (7.4%)	3 (6.8%)	
Autologous	2 (7.4%)	5 (11.4%)	
Type of haematological malignancy			0.447
Hodgkin lymphoma	0 (0.0%)	1 (2.3%)	
Non-Hodgkin lymphoma	11 (40.7%)	10 (22.7%)	
Chronic lymphocytic leukemia	3 (11.1%)	10 (22.7%)	
Acute lymphoblastic leukemia	1 (3.7%)	0 (0.0%)	
Acute myeloid leukemia	1 (3.7%)	2 (4.5%)	
Multiple myeloma	4 (14.8%)	11 (25.0%)	
Myelodysplastic syndrome	4 (14.8%)	6 (13.6%)	
Myeloproliferative neoplasm	2 (7.4%)	4 (9.1%)	
Smoker	9 (33.3%)	16 (36.4%)	0.373
Hypertension	16 (59.3%)	19 (43.2%)	0.227
Dyslipemia	11 (40.7%)	18 (40.9%)	0.999
Obesity (Body Mass Index > 30)	3 (11.1%)	11 (25.0%)	0.215
Chronic kidney disease	2 (7.4%)	5 (11.4%)	0.701
Diabetes	7 (25.9%)	10 (22.7%)	0.086
Heart failure	2 (7.4%)	4 (9.1%)	0.999
COPD	1 (3.7%)	0 (0.0%)	0.380
Asthma	1 (3.7%)	2 (4.5%)	0.999
Laboratory parameters (mean, SD)			
Neutrophils (<500 cells/μL)	4 (14.8%)	1 (2.3%)	0.066
Lymphocytes (<1000 cells/μL)	16 (59.3 %)	23 (52.3%)	0.243
C-RP (mg/dL)	139.3 (25.8)	93.7 (11.9)	0.117
Ferritin (mg/L)	13,989 (1600)	11,807 (18097)	0.680
LDH (U/L)	663.9 (219.3)	345.2 (20.0)	0.161
DD (ng/mL)	3505 (8812)	2521 (4551)	0.594
DIC	3 (11.1%)	1 (2.3%)	0.141
ARDS	25 (92.5%)	16 (36.3%)	**0.0001**
COVID-19 therapy			
Lopinavir/ritonavir	14 (51.9%)	26 (59.1%)	0.626
Beta Interferon	2 (7.4%)	7 (15.9%)	0.693
Remdesivir	1 (3.7%)	0 (0.0%)	0.380
Hidroxicloroquina	23 (85.2%)	40 (90.9%)	0.469
Tocilizumab	13 (48.1%)	11 (25.0%)	0.070
Inmunoglobulin	1 (3.7%)	0 (0.0%)	0.371
Anakinra	6 (22.2%)	1 (2.3%)	0.010
Systemic corticoids	23 (85.2%)	23 (52.3%)	**0.005**
ICU admission	7 (25.9%)	4 (9.1%)	0.090
HFNC	10 (37.0%)	4 (9.1%)	**0.005**
NIMV	5 (18.5%)	2 (4.5%)	0.097
MV	6 (22.2%)	4 (9.1%)	0.164

heterogeneous haematologic population, which prevents from drawing any conclusion about specific types of haematologic disease or specific haematologic therapies in relation to COVID-19 outcome. During the study period, at the beginning of the pandemic, patients who received steroids, remdesivir and tocilizumab did so in the setting of clinical trials, or off-label, as compassionate use. In the case of steroids and tocilizumab, their use was significantly inferior than in patients without hematological malignancy, probably for fear of increasing immunocompromise without the certainty of a beneficial effect. Only 1 case had access to remdesivir . In this respect the results may not be applicable to the current management of COVID-19. Patients included belong only to the first COVID-19 wave, when antibody detection during recovery was not systematically addressed, and consequently it was not possible to analyze. Our series includes only hospitalized patients with COVID-19 and the results cannot be generalizable to a wider population of non-admitted haematologic patients.

Our results suggest COVID-19 has worse outcomes in haematologic patients than in non-haematologic, independently of age, and that the development of ARDS and thrombotic complications drive the higher in-hospital mortality. Immune-compromise does not prevent inflammatory complications but may in addition impede viral elimination. Maximal stress in preventive measures in haematologic patients is warranted (Malek et al., 2021), and, if unfortunately infected, close surveillance with antiviral, anti-inflammatory and anticoagulant treatment before decompensation as well as prompt consideration of intensive care management in those deteriorating (Giesen et al., 2021).

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of Málaga on March 27, 2020 (Ethics Committee code: SEMI-COVID-19 27-03-20), as per the guidelines of the Spanish Agency of Medicines and Medical Products.

Consent for publication

Only patients who had previously given consent for their medical records to be used for medical research were included in this registry. Data confidentiality and patient anonymity were maintained at all times, in accordance with Spanish regulations on observational studies.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

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