ARTÍCULO ORIGINAL

Gac Méd Caracas 2021;129(2):279-291
DOI: 10.47307/GMC.2021.129.2.2

COVID-19: Hematological and laboratory findings in patients from a private hospital in Caracas, Venezuela. Correlation with mortality

COVID-19: Hallazgos hematológicos y de laboratorio en pacientes de un hospital privado de Caracas, Venezuela. Correlación con la mortalidad

Müller A[1,2], Soyano A[3], Chirinos L[1], Ochoa A[1], Guillermo P[1], William V[1], Ramírez I[1], Galea A[1], Comegna M[1], Ravard M[1], Otero K[1], Durán M[1], Piña J[1], Marcano H[1], Domínguez J[1], Serbanescu R[1], Ruiz F[1], Molina G[1], Flores M[1], Olivo E[1], Croce N[2]

SUMMARY

The first cases of COVID-19 in Venezuela occurred in mid-March 2020. The number of cases remained relatively low until May when it began to increase, reaching its maximum in August 2020. The purpose of this work is to present the clinical, hematological, and laboratory studies carried out on 139 patients hospitalized at the El Ávila Clinic, a private hospital in Caracas, between June 30 and September 15, 2020. The 139 patients (98 males, 41 females) had an average age of 62.7 years (range 31 to 91); 55 (39.8 %) patients presented worsening of their disease, for which they were transferred to the intensive care unit, where 41 (74.54 %) died. Most of these patients had comorbidities such as obesity, diabetes, and high blood pressure. Hematological and laboratory studies on admission are similar to those reported in similar studies in different parts of the world.

Keywords: *COVID-19 in Caracas, hematological parameters, COVID-19 mortality*

RESUMEN

Los primeros casos de COVID-19 en Venezuela ocurrieron a mediados de marzo de 2020. El número de casos se mantuvo relativamente bajo hasta mayo cuando comenzó a aumentar, alcanzando su máximo en agosto de 2020. El propósito de este trabajo es presentar la clínica, hematología y estudios de laboratorio realizados en 139 pacientes hospitalizados en la Clínica El Ávila, un hospital privado de Caracas, entre el primero de julio y el 20 de septiembre de 2020. Los 139 pacientes (98 hombres, 41 mujeres) tenían una edad promedio de 62,7 años (rango 31 a 91); 55 (39,8 %) pacientes presentaron empeoramiento de su enfermedad, por lo que fueron trasladados a la unidad de cuidados intensivos, donde fallecieron 41 (74,54 %). La mayoría de estos pacientes tenían comorbilidades

DOI: https://doi.org/10.47307/GMC.2021.129.2.2

ORCID: Müller A. 0000-0001-8421-4441; Soyano A. 0000-0002-0728-9295

[1]Clínica El Ávila, Caracas, [2]Razetti Medical School, Universidad Central de Venezuela; [3]Venezuelan Institute for Scientific Research (IVIC).
E-mail: asoyano@gmail.com, soyanolop@gmail.com

Recibido: 11 de febrero 2021. Revisado: 24 marzo 2021
Aceptado: 25 de marzo 2021

como obesidad, diabetes e hipertensión arterial. Los estudios hematológicos y de laboratorio al ingreso son similares a los reportados en otros estudios fuera de Venezuela.

Palabras clave: *COVID-19 en Caracas, parámetros hematológicos, COVID-19 mortalidad.*

INTRODUCTION

The new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) belongs to the beta group of the *Coronaviridae* family and is the causative agent of a multisystemic disease, called COVID-19, the third notorious zoonotic coronavirus disease after severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). COVID-19 has an incubation period of 1 to 14 days. Worldwide, as of January 8, 2021, 86 749 940 confirmed cases of COVID-19, including 1 890 342 deaths, had been reported (1). Venezuela in particular presents a peculiar situation that contrasts in several aspects with both the world and the Latin American situation. The first case was officially reported on March 13, 2020, but it was not until May when the number of cases began to increase without reaching the high figures of other neighboring South American countries (2,3). According to official public reports, by February 2, 2021, Venezuela had 127 752 cases of covid-19 with 1 202 deaths been, estimated mortality of 0.94 % (4). Patients with COVID-19 experience different manifestations of the disease ranging from asymptomatic infection to acute respiratory distress syndrome (ARDS) with pneumonia of varying severity, sepsis with multiple organ failure, and death (7). Guan et al. studied 1 099 laboratory-confirmed COVID-19 patients in 552 hospitals in China and showed that the mortality rate of non-severe (mild and moderate type) and severe (severe and critical type) patients were 0.1 % and 8.1 %, respectively (8). Yang et al. studied 52 critically ill COVID-19 patients and reported a mortality rate of 61.5 % (9). Two case series from the United States also reported a similar mortality rate of 50 % and 67 %, respectively, in critically ill COVID-19 patients (10,11). The general mortality rate reported for COVID-19 differs according to the country, due to the different health systems, prevention, and control measures applied in each of them: the USA with rates of 5.91 %, Spain with 10.06 %, the United Kingdom with 14.53 %, Italy with 13.95 % and Russia 16.41 % (12). According to reported data, the emerging coronavirus has crossed international borders, infecting more than thirty-seven million individuals causing millions of deaths (13). The clinical laboratory provides important information related to COVID-19 for the diagnosis, prognosis, and therapeutic response (14). The purpose of this work is to present the hematological and laboratory studies carried out on 139 patients admitted to a private hospital in Caracas (Clínica El Ávila), between July 1 and September 15, 2020, and to compare the laboratory findings between the deceased patients with survivors and mortality recorded in patients who were treated in the Intensive Care Unit (ICU). This is an observational, descriptive, and retrospective study.

MATERIAL AND METHODS

Patients. One hundred and thirty-nine (139) patients with clinical symptoms of COVID-19 with moderate to severe intensity were hospitalized at the El Ávila Clinic. The average age of all hospitalized COVID-19 patients was 62.7 years, with a range of 31-91 years. When broken down by age group, there were 35 patients (25.3 %) between 31 and 50 years-old, 55 patients between 51 and 70 years-old (39.8 %), and 48 patients over 70 years old (34.8 %). Of those patients, 55 had to be transferred to the ICU. Epidemiological, clinical, laboratory, and radiological parameters were obtained from these patients. Secondary infection was diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteremia and a positive culture for pathogenic bacteria was obtained from lower respiratory tract samples (sputum, bronchoalveolar lavage fluid, or endotracheal aspirate) or blood samples obtained after admission to the clinic. Complications during the ICU stay were recorded such as respiratory distress syndrome, kidney failure, sepsis, shock, acute liver failure, acute heart failure, neurological problems. Of the 139 hospitalized patients, 98 were discharged, according to the

following criteria: absence of fever for at least 3 days, evident improvement in both lungs on chest tomography, clinical remission of respiratory symptoms, and two pharyngeal smear samples negative for SARS-CoV-2 RNA obtained at least 24 hours apart.

Laboratory tests. All patients admitted to the Clinic underwent a real-time reverse transcription-polymerase chain reaction test for SARS-Cov-2. Nasal swab samples were collected to extract SARS-CoV-2 RNA from the patients. The real-time RT-PCR assay was performed using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's Solis BioDyne protocol. Initial clinical laboratory tests performed included a complete hematological profile with platelet count, serum biochemical tests (including liver and kidney function, creatine kinase, lactate dehydrogenase, a coagulation profile with prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer. Coagulopathy was defined as the difference in the prothrombin time of the control and that of the patient greater than 3 seconds or when the PTT was more than 6 seconds of the patient's activated partial thromboplastin time compared to the control. Hypoproteinemia was defined as a blood albumin concentration of less than 25 g /L. In addition, blood levels of ferritin were measured. Respiratory samples, including nasal and throat swabs, or sputum were tested to exclude the presence of other viral infections, such as influenza, respiratory syncytial virus, avian influenza, parainfluenza virus, and adenovirus.

Statistical analysis. The data were analyzed using the Statistical Package for Social Science (SPSS) version 17. The binary logistic regression model was used to determine the association between hematological abnormality and independent variables, and between survival and death among patients. Odds ratio (OR) and 95 % confidence interval (CI) were used to measure the strength of association; P-value <0.05 was considered as statistically significant.

RESULTS

One hundred and thirty-nine (139) patients with moderate, severe, or critically ill clinical manifestations of COVID-19 were hospitalized at El Ávila Clinic. All were positive for SARS-CoV-2 infection with the nasal swab RT-PCR test. The demographic data of these patients are presented in Table 1. Of these patients, 98 patients were male (70.5 %) and 41 patients were female (29.5 %). The composition by age groups differs in men and women. Only 12 % of hospitalized COVID-19 female patients are

Table I

Demographic characteristics of COVID-19 patients

		Total	Survivors	Deceased
No.		139	98 (70.5%)	41 (29.5%)
Age (years)	62.7			
Range	31 - 91			
31-50		39 (28.1%)	31 (31.6%)	8 (19.5%)**
51-70		51 (36.7%)	39 (39.8%)	12 (29.3%)**
>70		49 (35.3%)	28 (28.6%)	21 (51.2%)**
Male		98 (71%)	69 (71.1%)	29 (70.7%)
Female		41 (29%)	29 (28.9%)	12 (29.3%)
Mortality				
General		29.5%	(41 / 139)	
ICU		74.5%	(41 / 55)	

** P< 0.05

under 50 years old, while in male patients is 32 %. Forty-nine (49) percent of female patients are in the group of more than 70 years-old while in men it is 27 %. The differences were statistically significant ($P < 0.05$).

Fifty-five (55) patients were transferred to the Intensive Care Unit, where 41 (74.54 %) died. Of the 98 survivors, 69 were male (71.1 %) and 29 were female (28.9 %) and of the deceased patients, 29 patients were male (70.7 %) and 12 were female (29.3 %) being the general mortality of 29.5 %. When the group of deceased patients was broken down by age group, 8 patients (19.5 %) were from 31 to 50 years-old, 12 patients from 51 to 70 years old (29.3 %), and 21 patients over 70 years old (51.2 %), while in the survivors the age groups were 31 to 50 years old, 31 patients (31.6 %), from 51 to 70 years-old, 39 patients (39.8 %), and over 70 years, 28 patients (28.6 %). The most frequent symptoms upon admission of the 55 patients admitted to the ICU were fever in 33 patients (60 %), cough in 27 patients (49 %), general malaise in 25 patients (45.5 %), dyspnea in 14 patients (25.5 %), asthenia in 13 patients (23.63 %), myalgias in 6 patients (10.9 %), other symptoms that presented were: hyporexia, diarrhea, headache, anosmia, dysgusia, arthralgia, and odynophagia. The diagnosis was confirmed by real-time reverse transcriptase-polymerase chain reaction on a nasopharyngeal swab. Of the 139 hospitalized patients, 55 deserved to be transferred to the ICU (39.8 %) because they presented acute respiratory distress syndrome with a decrease in oxygen saturation < 90 %. Of the 55 patients admitted to the ICU, 97 % had acute respiratory distress syndrome of high severity and pneumonia. Comorbidities were present in the majority of critically ill patients admitted to the ICU (61.82 %). Forty-one (41) patients (74.5 %) died in the ICU. When analyzing the comorbidities of patients who died in the ICU, arterial hypertension was present in 26 patients (63.4 %), overweight was present in 16 patients (39.0 %), of which a 50-year-old patient had morbid obesity, and diabetes mellitus in 7 patients (17.1 %). Of those patients who were discharged alive from the ICU, 8 had hypertension, 5 had overweight, and 7 had diabetes mellitus. Hypertension and overweight were more frequent in patients who died (Table 2). Other comorbidities that these ICU patients presented were chronic renal failure (1 patient), heart disease (4 patients), chronic atrial fibrillation (1 patient), chronic obstructive pulmonary disease (1 patient), pulmonary fibrosis (1 patient), bronchial asthma (1 patient), hypothyroidism (2 patients), non-Hodgkin lymphoma (1 patient,) prostate carcinoma (3 patients), diverticular disease of the colon (1 patient), history of myocardial infarction (1 patient), history of cerebrovascular accident (1 patient). Other complications developed in ICU: septic shock (11 patients), acute renal failure (10 patients), arrhythmia (3 patients), ventricular tachycardia (2 patients), myocardial infarction (1 patient), arterial thrombosis (1 patient), hepatitis (1 patient). Among deceased patients, the median time from symptom onset to hospital admission was 6 days (range 1.0-24.0), which tended to be

Table 2

Comorbidities in ICU (55 patients)

	Admitted (55 patients)	Survivors (14 patients)	Deceased (41 patients)
Pathology*			
HBP (hypertension)	34 (61.8 %)	8 (57.1 %)	26 (63.4 %)
Obesity	21 (38.2 %)	5 (35.7 %)	16 (39.0 %)
Diabetes mellitus	14 (25.5 %)	7 (50.0 %)	7 (17.1 %)

*Note. Some patients had more than one pathology.

shorter than for patients recovered: 15 days (7.0-25.0). The median time from onset of symptoms to death in deceased patients was 20 (1-42) days, and the median time from first symptoms to discharge in recovered patients was 15 (7-25) days. The median length of stay in the ICU for deceased patients was 11 days (1-31).

The leukocyte count (expressed in number of cells /L) upon admission of the 139 patients was 8.8 ± 5.1 x 10^9 / L, with 14 patients presenting leukopenia of less than 4.5 x 10^9 / L and 4 patients leukopenia of less than 3.5 x 10^9 / L. The mean differential count was: neutrophils 6.9 ± 1.2 x 10^9 / L, lymphocytes 1.3 ± 1 x 10^9 / L, monocytes 0.48 ± 0.3 x 10^9 / L. Of the 41 patients with COVID-19 who died, the leukocyte count was: 10.4 ± 6.0 × 10^9 / L, (of these 18 patients had leukocytosis with a white count ≥ of 10 × 10^9 / L and only 2 patients had leukocytosis of ≥20 × 10^9 /L). The differential count of the leukocytes of the deceased patients showed: neutrophils: 8.7 ± 0.9 x 10^9 / L, lymphocytes: 1.4 ± 0.6 x 10^9 / L, monocytes: 0.6 ± 0.4 x 10^9 / L. Lymphopenia occurred in 20 patients (48.78 %) of the deceased with values of < 0.5 x 10^9 /L in 17 patients (41.46 %) and values of < 1 x 10^9 /L in 3 patients. The surviving COVID-19 patients showed the white blood cell count at 8.13 ± 4.5 x 10^9 /L. The differential white blood cell count of the survivors showed: neutrophils: 7.3 ± 1.6 x 10^9 /L, lymphocytes: 1.8 ± 1.2 x 10^9 / L, monocytes: 0.7 ± 0.6 x 10^9 /L. There was no lymphopenia in the survivors (Table 3). The observation of the blood under a light microscope showed morphological abnormalities in the blood of 90 % of the patients: hyposegmentation of neutrophils, toxic granulations, Howell-Jolly bodies, abnormalities in pseudo-Peger-Huet neutrophils (neutrophils with hyposegmented nucleus and lack of primary granulations), Dohle bodies (peripheral inclusions in neutrophils made up of remnants of the endoplasmic reticulum). In the lymphoid series, the presence of large granular lymphocytes, plasmacytoid and atypical lymphocytes was observed. In monocytes, the presence of one or more large coalescing vacuoles in the cytoplasm was observed, as well as the presence of vacuoles in eosinophils. The most uniform morphological finding was cytoplasmic vacuolization with large coalescing vacuoles in 80 % of monocytes and smaller vacuoles in 85 % of neutrophils, 40 % of lymphocytes, and 10 % of eosinophils (13 %). Neutrophil hyposegmentation was present in 70 % of the patients, attracting a lot of attention along with the vacuolization of the cells. Neutrophil toxic granulation was quite common (90 %), as well as the presence of atypical lymphocytes and large granular lymphocytes (70 %). The hemoglobin of

Table 3

Hematologic parameters of patients with COVID-19

		Hospitalized (139 patients)	ICU Survivors (14 patients)	Deceased (41 patients)
Leucocytes	(10^9/L)	8.8±5.1	8.13±4.46	10.4±6.04**
Neutrophils	(10^9/L)	6.9±1.2	7.3±1.6	8.7±0.9**
Lymphocytes	(10^9/L)	1.3±1.0	1.8±1.2	1.4±0.6**
Monocytes	(10^9/L)	0.48±0.3	0.7±0.6	0.6±0.4
Hemoglobin (g/dL)		13.5±2.8	14.95±1.34	13.26±2.12
Hematocrit (%)		40.15±5.17	40.01±5.41	40.2±4.98
Platelets	(10^9/L)	235±89.4	250±102.56	219±74,3

** P < 0.05

the 139 patients was 13.5 ± 2.8 g/dL, hematocrit 40.15 ± 5.17 % (18 patients had anemia with Hb between 9.4 ± 2.4 g/dL and hematocrit of 37.4 ± 8.2 %). The hemoglobin's of the deceased patients were 13.26 ± 2.12 g / dL, hematocrit 40.2 4.98 % (8 patients of the 41 deceased had anemia on admission with hemoglobin between 10.3 and 11.8 g / dL) and that of the survivors was 14.95 ± 1.34, hematocrit 40.01 ± 5.41 % (16 patients of these survivors had anemia on admission with Hb between 8.6 and 11.8 g / dL and of these 4 patients with hemoglobin between 8.6 and 9.7 g / dL) (Table 3). The platelet count in the 139 patients was 235 ± 89.4 × 10^9 / L (10 of the patients had thrombocytopenia on admission, with values from 64 to 139 × 10^9 /L) and only 2 patients had thrombocytosis of 619 and 623 × 10^9/L. The platelet count of the deceased was 219 ± 74 × 10^9/L and of the survivors, 250 ± 102 × 10^9 / L. Of the 41 deceased patients, only 2 presented thrombocytopenia of 114 and 129 × 10^9/ L on admission. Survivors upon admission had thrombocytopenia, only 5 of them with counts from 64 to 125 × 10^9 / L (Table 3). In relation to the coagulation tests performed, the prothrombin time (PT) of the 139 admitted patients was 14.5 ± 1.7 sec. (controls 12.4 ± 0.04), only three patients of the 139 patients admitted with COVID-19 had increased PT without taking an anticoagulant. The PTT of the 139 patients admitted with COVID-19 was 30.3 ± 5 sec. (controls 28.9 ± 4), 3 patients had increased PTT upon admission without taking an anticoagulant. All deceased patients and survivors presented average normal PTT on admission. Dimer D: 5,695 ± 16,864 ng/mL (normal value <0.5). Deceased 0.15 ± 15.5, survivors 0.95 ± 0.6. (Table 4). Other laboratory tests of the 139 patients showed plasma creatinine levels at admission: 1.44 ± 3.1 (NV 0.84-1.21 mg/dL). 10 patients had elevated creatinine values, 5 of them with values lower than 1.7 mg%, and 5 of them with values between 6.29 and 28.7 mg% due to kidney failure. Only 3 of the deceased patients had a slight increase in creatinine upon admission and 7 of the survivors had plasma creatinine values of 1.61 mg% to 28.7 mg. The 139 patients presented serum ferritin values of 1068.44 ± 1 087.82 ng/mL (NV 20-140 ng/mL) at admission, patients who died on admission presented serum ferritin values of 1 265.76 ± 1 430.9 ng/mL, and those who discharged live 955 ± 789.05 ng/mL (Table 5). C-reactive protein was at plasma levels of 17.60 ± 73.1 mg/dL (NV 0-0.9 mg/dL) in the 139 patients admitted with COVID-19, only 5 % of patients had C-reactive protein in normal values and in the deceased patients they had values of 16.54 ± 22.71 mg/dL and in the survivors in 8.93 ± 8.67 mg/dL.

To determine if there was any difference in the mortality rate according to the period of admission to hospitalization, two cohorts were formed: the one who was admitted in the first part of the epidemic outbreak (from July 1st. to August 10; 85 patients) and the one who was admitted in the second part (from August 11 to 20

Table 4

Coagulation tests in COVID-19 patients

Number	Hospitalized (139 patients)	ICU Survivors (14 patients)	Deceased (41 patients)
Prothrombin Time (sec.)			
Controls	12.47±0.1	12.46±0.1	12.46±1.0
Patients	13.47±1.7	13.52±1.4	13.31±0.1
Ratio	1.09±0.14	2.24±5.78	1.12±0.21
PTT (sec.)			
Controls	28.9±0.3	29.17±0.74	28.10±3.90
Patients	30.5±5	28.74±9.19	30.61±2.7
Difference	1.25±4.26	1.52±4.72	0.51±2.2
Dimer D (ng/mL)	1.96±3.04	2.19±4.97	6.07±15**

** $P < 0.05$

Table 5

Other laboratory biomarkers in COVID-19 patients

	Hospitalized (139 patients)	ICU Survivors (14 patients)	Deceased (41 patients)
Ferritin (ng/mL)	1 068.44±1 087.82	955.4±789.05	1 265±1 430.9**
Creatinine (mg/dL)	1.44±3.14	1.68±3.67	0.94±0.25
C Reactive Protein (mg/dL)	17.60±73.10	8.93±8.67	16.54±23.41**

** $P < 0.05$

September, 54 patients). Although the mortality rate was lower in the second group, the values were not statistically significant (29 % vs 25 %, $P > 0.05$). Changes in hematological parameters were similar in both groups.

DISCUSSION

Of the 139 patients hospitalized with COVID-19 at Clínica El Ávila (Caracas, Venezuela), the majority (71 %) were male. This is consistent with the publications on the frequency of COVID-19 in patients according to sex (8,15-17). Evidence of sex-related differences in severity of COVID-19 emerged in China, where hospital admissions and mortality were higher among men than among women (8,15-17). Scully et al. report a male bias in mortality from COVID-19 in 37 of the 38 countries that have provided sex-disaggregated data (16). In this study, Of the patients who died, 29 patients were male (70.7 %), and 12 female (29.3 %). A similar trend has been observed in Venezuela (3). Analysis carried out shows that the average male mortality rate in 38 countries is 1.7 times higher than the female ($P < 0.0001$) (male 7.3 (95 % CI, 5.4-9.2); female mortality rate 4.4 (95 % CI, 3.4-5.5), which is in agreement with other reports (18,19). COVID-19 data from Italy, Spain, Germany, Switzerland, Belgium, and Norway reveal that, among all age groups older than 20, mortality rates are higher in men than in women (18). Biological sex affects differentially, the aging of the immune system (19), and the severity of COVID-19 infection in males is probably due in part to the difference in concentrations of sex steroids (20). In addition to reduced concentrations of sex steroids, an age-related mosaic loss of the Y chromosome in leukocytes can alter the transcriptional regulation of immunoregulatory genes (21). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as an entry receptor (22). The ACE2 gene is located on the X chromosome which is regulated by estrogens (23) and exhibits tissue-specific expression patterns (24). Differences in ACE2 expression may be due to differential sex expression of ACE2 variants (25-27). ACE2 is associated with the expression of the interferon gene, which in turn shows sex-specific regulation (28,29). The average age of all COVID-19 patients in this series was 62.7 years, with a range of 31 to 91 years. In a series of 138 patients from Wuhan, China, Li et al. reported that the mean age was 62 ± 14 years (30). When breaking down our patients by age groups, we had 48 patients over 70 years old (34.8 %). In March 2020 in Italy, 22 512 COVID-19 patients were reported with an average age of 64 years similar to the patients in this study (31). Between the end of March and the end of May, the incidence of COVID-19 was highest among adults aged 80 and over, with a peak in incidence in the week beginning April 12. In June, incidence increased in all age groups, with the fastest rate of increase and the highest overall incidence among young adults ages 18 to 24; the rate in this group remains the highest among all age groups. Between late September and early October, the weekly incidence decreased among young adults ages 18 to 24 only and then continued to increase steadily across all age groups through November

14. The proportion of people older than 70 years among confirmed cases of SARS-CoV-2 differed markedly between countries, ranging from 4.9 % to 40.4 %. There was a strong linear association between the proportion of people older than 75 years and country-specific mortality rates (32). Data from 20 European countries and the USA and Canada showed that the variation in the crude death rate of COVID-19 is predominantly determined (80-96 %) by the proportion of older people diagnosed with SARS-CoV-2. The age distribution of SARS-CoV-2 infections is still far from homogeneous. Detailed demographic data should be taken into account in all analyzes on COVID-19-associated mortality (33). Advanced age and male sex are risk factors for a worse prognosis in patients with COVID-19. While men and women have the same susceptibility to SARS-CoV-2, men may be more likely to have greater severity and mortality regardless of age and susceptibility (34).

The most frequent symptoms upon admission to hospitalization were fever and cough, followed by sputum production and fatigue, as has been reported in different studies of COVID-19. Huang reported, in a group of 41 patients, that the most common symptoms at the onset of the disease were fever (98 %), cough (76 %), and myalgia or fatigue (44 %); less common symptoms were sputum production (11 out of 39 [28 %]), headache (3 out of 38 [8 %]), hemoptysis (2 out of 39 [5 %]), and diarrhea (1 out of 38 [3 %]). More than half of the patients (22 out of 40 [55 %]) developed dyspnea (8,9,12, 35,36). Regarding the comorbidities of patients with COVID-19, hypertension (high blood pressure), overweight and diabetes mellitus were the most frequent, prevailing in patients who died, which coincides with international reports. Clinical studies conducted in different countries showed that obesity and type 2 diabetes are associated with severe forms of COVID-19 in all ethnic groups studied. In the USA, 5 700 hospitalized patients with severe forms of COVID-19 were reported to have obesity (41 %) or type 2 diabetes mellitus (33 %) (37). According to the results obtained in China, individuals with obesity compared to patients with normal weight have significantly more severe forms of COVID-19 (38). A meta-analysis based on 33 studies revealed that type 2 diabetes is associated with mortality and severity of COVID-19 (39). A retrospective study of 1 158 hospitalized patients in Kuwait revealed that patients with morbid obesity and type 2 diabetes mellitus were more likely to be admitted to the intensive care unit (40). Statistically significant correlations were found between the prevalence of obesity and the number of total deaths of patients with COVID-19 in several different countries (41). In this study, only one patient with morbid obesity was observed and he died. Bardaran et al. analyzed 33 studies (32 in China and one in Taiwan) and reported that the most prevalent finding in patients with COVID-19 was hypertension, which was found in 21 % of patients (42). Other prevalent findings were: diabetes mellitus (11 %), cerebrovascular disease (2.4 %), cardiovascular disease (5.8 %), chronic kidney disease (3.6 %), chronic liver disease (2.9 %), chronic lung disease (2.0 %), malignant neoplasia (2.7 %), and smoking (8.7 %). In a meta-analysis of 7 studies and 1,546 patients, Yang et al. reported that the most prevalent comorbidities were hypertension (21.1 %, 95 % CI: 13.0-27.2 %) and diabetes (9.7 %, 95 % CI: 7.2-12.2 %), followed by cardiovascular disease (8.4 %, 95 % CI: 3.8-13.8 %) and respiratory disease (1.5 %, 95 % CI: 0.9-2.1 %) (43). In our series of patients admitted to the ICU, the most prevalent comorbidity was hypertension (61.8 %), followed by obesity (38.2) and diabetes (25.5 %). Differences in leukocyte, neutrophil, and lymphocyte counts were observed between deceased patients and survivors. Of the 139 patients, 14 had leukopenia of less than 4.5 x 10^9/ L, of which in 4 it was less than 3.5 x 10^9 / L. Leukopenia on admission was also reported by Huang et al. in 25 % of its 40 patients (less than 4×10^9 / L) (36). Zhang showed that in 140 hospitalized patients 19.6 % had leukopenia. Wang demonstrated in a review of patients with COVID-19 the presence of 33 % of leukopenias (44). In other studies, leukopenia has been reported to be between 28.1 % and 68.1 %, depending on the severity of the disease and the underlying pathology, suggesting a possible association between severity of leukopenia and severity of COVID-19 (44-47). Of the 41 patients with COVID-19 who died, the leukocyte count on admission was: $10.8 \pm 6.2 \times 10^9$ / L, (of these 18 patients had leukocytosis with a white count $\geq 10 \times 10^9$ / L and only 2 patients had leukocytosis $\geq 20 \times 10^9$ / L).

Leukocytosis in the deceased was more prevalent than in the survivors. Leukocytosis, regardless of type (neutrophilia, lymphocytosis, or both), is seen in a minority of COVID-19-infected patients and appears to herald a bacterial infection or a superinfection. A meta-analysis of the existing literature identified leukocytosis in 11.4 % of patients with severe disease compared with 4.8 % in patients with mild to moderate disease (odds ratio [OR], 2.54; confidence interval [CI] 95 %, 1.43-4.52) (14). The differential count of the leukocytes of the deceased patients showed neutrophils: 8.7± 0.9 x 10^9 / L, lymphocytes: 1.4 ± 0.6 x 10^9 / L, monocytes: 0.6 ± 0.6 x 10^9 / L. The surviving COVID-19 patients showed a leukocyte count at the admission of 7.35± 3.6 x 10^9 / L. The differential count of the leukocytes of the survivors showed neutrophils: 7.3± 1.6 x 10^9 / L, lymphocytes: 1.8 ± 1.2 x 10^9 / L, monocytes: 0.7± 0.6 x 10^9 / L. In this study, neutrophilia was higher in the patients who died compared to the survivors ($P < 0.05$). It has been reported that the count and percentage of neutrophils are significantly higher in severe and critical COVID-19 patients (48-50). Available data suggest that neutrophilia is an expression of the cytokine storm and hyperinflammatory state that have an important pathogenic role in COVID-19 (51-53). Neutrophilia may also indicate associated bacterial infection (54). The differential count of these 139 patients at admission showed monocytes 0.48 ± 0.3 x 10^9 / L and the monocytes of the deceased: 0.6 ± 0.4 x 10^9 / L. Zhang et al. did not report quantitative alterations in patients with COVID-19 in relation to healthy individuals. However, they observed significant differences in monocyte morphology in COVID-19 patients as in this study (7). Lymphopenia occurred in 20 patients (48.78 %) of the deceased group with values of < 0.5 x 10^9 / L in 17 patients (41.46 %) and < 1 x 10^9 / L in 3 patients. No lymphopenia was observed in the survivors. Lymphopenia is a common finding in patients with COVID-19 infection and is believed to represent a defective or dysregulated immune response to the virus (54). Huang et al. noted that lymphopenia (defined as an absolute lymphocyte count <1.0 × 10^9 / L) was observed in 26 (63 %) of the patients (43). A meta-analysis found lymphopenia in 35 % to 75 % of patients and that lymphopenia was a more common feature of patients who died from the disease (55). In South Africa, a study of 102 patients reported lymphopenia with an absolute lymphocyte count <1.0 × 10^9 / L in 49 (48.0 %) patients and severe lymphopenia of <0.5 × 10^9 / L in 19 (18.6 %) (56). Several studies have reported lymphopenia in 40 to 91.6 % of patients suggesting that lymphopenia can be used as a prognostic factor for COVID-19 (57). Fan et al. reported in a study of 67 patients lymphopenia in 24 patients (36.9 %) with 19 having moderate lymphopenia (absolute lymphocyte count [ALC] 0.5-1 × 10^9/L), and five with severe lymphopenia (ALC < 0.5 × 10^9/L. They identified, that a lymphocyte count of <0.6 × 10^9/L is predictive of admission to the intensive care unit (ICU) (58). Although some of the patients had anemia, it was detected at the beginning and was not attributable to COVID-19. The development of anemia could be due to myelosuppression due to infection or frequent blood collection for laboratory studies. Huang et al. detected in patients with COVID-19 an increase in inhibitory interleukins such as IL-4 and IL-10 that could be responsible for the inhibition of erythropoiesis and lymphopoiesis (43). Only 10 out of the 139 patients studied had thrombocytopenia on admission. Thrombocytopenia was observed in survivors in 5 of them with counts of 64 to 125 × 10^9 / L. Only 2 patients of the 41 who died presented thrombocytopenia of 114 and 129 × 10^9 /L on admission. Thrombocytopenia as a manifestation of COVID-19 has been reported between 5 and 40 % of patients (59-62). Several mechanisms of thrombocytopenia in COVID-19 have been proposed: the direct or indirect effect of SARS-CoV-2 on hematopoietic and endothelial cells, which may be associated with impaired megakaryocyte maturation, increased platelet aggregation, platelet activation, and, consequently, platelet consumption in the microcirculation of damaged lung tissue (63). Only 2 patients in this study presented thrombocytosis at the admission of 619 and 623 × 10^9/L. Morphological abnormalities of neutrophils, monocytes, lymphocytes, and eosinophils have been previously described in COVID-19, such as immaturity traits, dysmorphism, and apoptotic degenerative morphology (64). The cytoplasmic and nuclear morphological abnormalities observed, from hyposegmented nuclei to apoptosis, in circulating granulocytes at the time of hospital admission have been correlated with

the hyperinflammatory state due to the cytokine storm and usually precede the increase in reactive lymphocytes (65). In relation to the coagulation tests performed, the PT of the 139 patients on admission was normal in all cases and the PTT was prolonged on admission in only 3 patients. D-dimer values were greater than 1 μg / mL at admission in 45 (32 %) patients. Patients who died in the ICU presented frequent elevation of the D-dimer (74 %) with values between 1.1 and 13.4 μg / mL. Surviving patients had D-dimer values of 0,95 μg /mL ± 2,9 μg /mL. The difference between survivors and deceased patients was statistically significant. The elevation of the D-dimer in COVID-19 has been reported by several authors (43,55,58,63). Zang et al. reported that the optimal cut-off value for D-dimer to predict hospital mortality in 343 patients was 2.0 μg / mL with a sensitivity of 92.3 % and a specificity of 83.3 %. Patients with D-dimer levels ≥ 2.0 μg / mL had higher mortality compared to those with D-dimer levels <2.0 μg / mL (65). Long et al. studied 115 hospitalized patients with COVID-19 and found that the bleeding disorder occurred in the early stage of COVID-19 infection, with 50 (43.5 %) patients having increased D-dimer and 74 (64.3 %) patients who had an increase in plasma fibrinogen levels. Among the 23 patients who died, 18 had an increase in D-dimer on admission. The authors conclude that coagulation dysfunction is more likely to occur in critically ill patients. D-dimer and prothrombin time could be used as significant indicators to predict COVID-19 mortality (66). Tang et al. reported that patients with COVID-19 had a worse prognosis when their blood clotting parameters (prothrombin time and activated partial thromboplastin time) were prolonged, had elevated levels of D-dimer and fibrin degradation products (FDP) abnormal, and antithrombin activity was lower than normal standards (67).

Other laboratory tests of the 139 patients showed plasma creatinine levels upon admission: 10 patients had elevated creatinine values, 5 of them presenting values less than 1.7 mg% probably due to dehydration, and 5 of them with values between 6.29 and 28.7 mg% due to pre-COVID-19 renal failure. Only 3 of the deceased patients had a slight increase in creatinine upon admission and 7 of the survivors had plasma creatinine values of 1.61 mg% to 28.7 mg%. There was no correlation between the degree of renal failure and mortality ($P > 0.05$). With regard to serum ferritin, all the deceased patients except for 3 of them presented elevated serum ferritin. Of the 139 patients admitted with COVID-19, only 5 had ferritin levels in the normal range, that is, 95 % of these patients had hyperferritinemia at admission and 38 of the 41 deceased had hyperferritinemia. Ferritin and C-reactive protein are considered as markers of an acute inflammatory reaction and as contributing factors to the hypercytokinemia syndrome believed to be responsible for the severity of COVID-19. A direct association between ferritin concentrations and the severity of the disease has been reported; Likewise, a higher concentration of ferritin has been observed in patients who died with COVID-19 compared to those who survived. A similar association was observed in this study (68,69). C-reactive protein was elevated in 95 % of the 139 patients admitted with COVID-19 and was higher in the deceased. This has been previously reported by Guan et al. (8).

In conclusion, the patients with COVID-19 admitted to a private hospital in Caracas (Clínica El Ávila) presented clinical and laboratory manifestations similar to those reported in other studies conducted outside of Venezuela. Likewise, the evolution of the disease is comparable with most other reports, indicating that we are dealing with the same disease. However, this clinical behavior of the disease contrasts with the epidemiological behavior (according to the official data reported daily by the National government) that indicate a low incidence of cases and low general mortality (ca. 0.8 %) (ref. 4), a phenomenon for which we do not have a satisfactory explanation.

ABBREVIATIONS

ALC: absolute lymphocyte count; CI: Confidence Interval; FDP: fibrinogen degradation product; Hb: hemoglobin; HBP: high blood pressure; Ht: hematocrit; ICU: Intensive Care Unit; PT: prothrombin time; PTT: partial thrombin time; NV: normal value.

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