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Clinical characteristics and evolution of pediatric patients with acute leukemia and SARS-COV2 virus infection in a third level hospital in Mexico

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ABSTRACT

Introduction: Reports have revealed that people susceptible to severe forms of COVID-19 are older adults with comorbidities; However, the pediatric population has also been affected, considering children with underlying conditions such as onco-hematological conditions to be high risk. We present a cases series in a third level hospital.
Material and methods: We conducted a retrospective study in children under the age of 16 years with a diagnosis of acute leukemia and infection with the SARS-CoV2 virus. Descriptive statistics with means and percentages were used. To show differences between the groups, Chi-square test, Student t test and Mann-Whitney U test were used depending on the type of variable and its distribution.
Results: SARS-CoV2 virus infection was confirmed in 15 children diagnosed with acute leukemia, at different stages of treatment. The mean age was 7.5 years, 8 male and 7 female, 11 of them diagnosed with acute B-cell lymphoblastic leukemia, one with acute T-cell lymphoblastic leukemia and 3 with acute myeloid leukemia. The mean days of hospital stay at the diagnosis of COVID-19 was 22. Thirteen of the children had fever and neutropenia. 7 patients died. There was a statistically significant correlation with the outcome in patients who presented a prolongation of aPTT, an increase in D-dimer, an increase in liver enzymes and severe respiratory distress with the need for mechanical ventilation.
Conclusion: The risk of death in children with leukemia and COVID-19 was associated with prolonged aPTT, increased D-dimer, increased liver enzymes, respiratory distress, and the need for mechanical ventilation.

1. Introduction

In December 2019, health authorities in China reported cases of severe viral pneumonia of unknown origin that were epidemiologically linked to the seafood market in Wuhan. Sequencing of samples from the respiratory tract revealed a new coronavirus. The disease was later named coronavirus-19 disease (COVID-19) and the virus was named SARS-CoV2 (severe acute respiratory syndrome due to coronavirus [1]. SARS-CoV-2, a single-stranded RNA

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B. Sánchez-Jara, A.R. Torres-Jiménez, M.A. Del Campo-Martinez et al.

Pediatric Hematology Oncology Journal 6 (2021) 42—48

virus, enters cells through the structural protein (protein S) that binds to the angiotensin-converting enzyme receptor 2 (ECA2). On March 11, 2020, the WHO made the pandemic declaration [2]. In less than 3 months from the first identified cases, the infection spread to at least 200 countries and on May 18, 2020, its distribution was reported worldwide [3]. Reports indicate that older males with comorbidities have more serious complications [4]. As of July 20, 2020, 14, 608, 517 cases have been reported worldwide. In Mexico, 344,224 confirmed cases and 39,184 deaths have been reported [5]. Children have accounted for about 2% of diagnosed cases in China, 1.2% of cases in Italy, and 5% of cases in the United States. The pediatric population considered high risk for severe forms of COVID-19 includes children with underlying conditions such as congenital heart defects, respiratory tract abnormalities, severe malnutrition, decreased hemoglobin levels, immunodeficiency, and immunocompromised states, such as the case of children with onco-hematological disorders [6].

In the pediatric hematology service of the General Hospital of the National Medical Center La Raza of the Mexican Social Security Institute (IMSS), we diagnose an average of 100 new cases of leukemia per year, of which 15 correspond to acute myeloid leukemia (AML) and 85 to acute lymphoid leukemia (ALL). Although these patients are considered a high-risk population, the data that specifically refers to this population remains limited. We present the clinical characteristics and evolution of pediatric patients diagnosed with acute leukemia and SARS-CoV2 virus infection in our unit, in May 2020.

2. Material and methods

We performed a retrospective study of the clinical, laboratory and radiological characteristics of 15 pediatric patients diagnosed with acute leukemia, hospitalized in the pediatric hematology service the General of the National Medical Center La Raza of the IMSS in which SARS-CoV2 infection was confirmed by real-time polymerase chain reaction (RT PCR). Patients under 16 years of age, diagnosed with acute leukemia, who were at different stages of treatment were included. The cases were initially diagnosed based on the clinical manifestations and exposure history. Suspicious cases were identified if a child had any of the following conditions: fever, respiratory or digestive symptoms or abnormal chest x-ray image.

In all patients, infection with SARS-CoV 2 virus was confirmed by RT-PCR. The classification of the images of lung CT was based on the CO-RADS score, that evaluates the suspicion of pulmonary compromise by COVID-19 on a 0 to 5 scale. CO-RADS 0 is set if none of the five categories can be assigned due to incomplete or insufficient quality scans. CO-RADS 1 is a very low level of suspicion. CO-RADS 2 implies a low level of suspicion. CO-RADS 3 includes equivocal findings for COVID-19 lung involvement that can also be found in other viral pneumonias or non-infectious etiologies. CO-RADS 4 implies a high level of suspicion showing some overlap with other viral pneumonias. The findings are similar to CO-RADS 5, but are not in contact with the visceral pleura or are unilateral. CO-RADS 5 implies a very high level of suspicion of lung involvement by COVID-19 based on typical CT findings. CO-RADS 6, was introduced to indicate proven COVID-19 as indicated by a positive RT-PCR test for SARS-Cov2 [7]. Data of clinical characteristics, laboratory and radiological studies, clinical evolution and outcome of the patients were collected. Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25). Descriptive statistics were performed with frequencies and means. Comparisons of values between groups were performed using a Chi square test, Student's t-test, or a Mann-Whitney U test according to the distribution and variable type, p value of less than 0.05 was considered

statistically significant. OR was calculated with 95% CI for nominal variables.

3. Results

The General Hospital National Medical Center La Raza of the IMSS, is a third-level hospital that cares for the pediatric and adult population, and in April 2020 it was converted into a hybrid hospital for the care of patients with COVID-19. The first case diagnosed with COVID-19 in our department was in a 13-year-old female patient, who had a 6-day hospital stay and a diagnosis of B-cell acute lymphoblastic leukemia (B-ALL), receiving remission-inducing chemotherapy. She developed a clinical picture characterized by fever, nasal discharge, dry coughing, headaches and abdominal pain. Chest radiography showed ground glass image and condensation areas, thus a nasal swab was taken to look for SARS-CoV2 infection by PCR-RT which turned out to be positive. Chest computed tomography (CT) showed ground glass image in the upper lobe of the right lung, requiring only supplemental oxygen supply. Due to the identification of a positive case, the children with whom she shared the room were considered contacts and suspicious cases are patients with fever, respiratory or digestive symptoms, or with an abnormal chest radiograph image. Table 1 shows the general characteristics of the patients, who were diagnosed in the period from May 8 to May 28, 2020, in which the index case and last case was identified.

We included 15 patients, with a mean age of 7.5 years, 8 male and 7 female, 11 of them diagnosed with B-ALL, one with T-cell acute lymphoblastic leukemia (T-ALL) and 3 with acute myeloid leukemia (AML). Thirteen of the children were on chemotherapy regimen (remission induction, reinduction and consolidation) and 2 on palliative chemotherapy for refractory leukemia. The mean days of hospital stay prior to COVID-19 diagnosis was 22 days, with a minimum of 6 and a maximum of 58 days. Thirteen patients (86.7%) had fever and neutropenia at the time of COVID-19 diagnosis. Seven patients died. Fig. 1 shows the survival table. The clinical characteristics associated with COVID-19 were rhinorrhea: 13.3% (N = 2), cough 60% (N = 9), headache 26.7% (N = 4), respiratory distress 53.3% (N = 8), seizures 6.7% (N = 1), irritability 26.7% (N = 4), drowsiness 13.3% (N = 2), odynophagia 13.3% (N = 2), diarrhea 13.3% (N = 2), refusal of food 13.3% (N = 2), cyanosis 6.7% (N = 1) and pharyngeal hyperemia 20% (N = 3). On physical examination of the chest, rales were found in 33.5% (N = 5), hypoventilation 46.7% (N = 7) and condensation syndrome in 13.3% (N = 2). In the blood cytometry parameters at the diagnosis of COVID-19, 86.7% had anemia (N = 13) with a mean of 9.2 g/dL (7.4—12.3 g/dL), leukopenia 86.7% (N = 13) with mean of 3760/mm2 (40—34840/mm2), lymphopenia 93.3% (N = 14), with a mean of 499/mm3 (range 20—2012/mm3), 80% of the patients showed neutropenia (N = 12), with an average of 2096/mm3 (range 0—26516/mm3). 66.7% had monocytopenia, mean of 726/mm3 (range 0—6280/mm3) (N = 10) and 86.7% (N = 13) showed thrombocytopenia with a mean of 8333/mm3, (range 4000—615,000/mm3).

When performing the statistical analysis on the coagulation studies, the prolongation of the activated partial thromboplastin time (aPTT) was significantly correlated to death, with a mean of 29.9 s (sec) in the surviving patients and in the patients who died of 35.75 s (p = 0.010) (Table 2), as well as an increase in D-dimer, with a mean in surviving patients of 407 ng/mL (range 289—562 ng/mL), and 4180 ng/mL (range 582—11183 ng/mL) in those who died (p = 0.010) (Table 2).

There were no significant changes in blood chemistry. In liver function tests, an increase in aminotransferases was found in the patients who died, with a mean of ALT of 70.8U/L for living patients

B. Sánchez-Jara, A.R. Torres-Jiménez, M.A. Del Campo-Martinez et al.

Pediatric Hematology Oncology Journal 6 (2021) 42–48

Table 1
General characteristics of the patients.

Patient	Age (years)	Sex	Diagnosis	Disease status	Chemotherapy administered	Days from chemotherapy administration to COVID-19 diagnosis	Clinical characteristics associated with COVID-19	Chest Radiography	Chest CT CORAD	Mechanical ventilation	Outcome/factors associated with morbidity and mortality
1	11	F	ALL B	C	Memorial Sloan-Kettering New York-II Consolidation	17	Fever, headache	Ground glass	5	–	Alive/no
2	7	M	ALL T	IR	CMR 02-16	31	Fever	Ground glass	3	–	Alive
3	3	M	ALL B	IR	CMR 02-16	18	Fever, irritability	Ground glass and condensation areas	–	–	Alive/urosepsis by *Enterococcus gallinarum*
4	12	M	ALL B	IR	CMR 02-16	10	Fever, cough, shortness of breath, cyanosis, cracking rales	Ground glass and condensation areas	–	Yes	Dead/tumor lysis syndrome, hemodialysis, *Enterobacter clocae* sepsis.
5	14	M	ALL B	RIR	IDA-FLAG	14	Respiratory distress	Ground glass and condensation areas	–	–	Alive/no
6	1	M	ALL B	IR	CMR 02-16	21	Fever, cough, irritability	Ground glass and condensation areas	–	Yes	Dead/urosepsis by *Candida albicans*
7	13	F	ALL B	IR	CMR 02-16	5	Fever, cough, headache, respiratory distress, odynophagia, abdominal pain rhinorrhea	Ground glass and condensation areas	4	–	Alive/no
8	9	F	AML	IR	CMR 09-14	25	Fever, rhinorrhea, cough, odynophagia, diarrhea	Normal	2	–	Alive/no
9	2	F	ALL B	R/R	Palliative chemotherapy	20	Fever, cough, respiratory distress, seizures, irritability	Ground glass and condensation areas	–	Yes	Dead/palliative treatment, massive infiltration to abdominal organs.
10	12	M	AML	IR	CMR 09-14	19	Fever, respiratory distress, abdominal pain, cracking rales	Condensación	2	Yes	Dead/Complicated appendicitis, septic shock.
11	9	F	ALL B	RIR	Memorial Sloan Kettering New York-II Induction	25	Fever, cough, headache, respiratory distress, crackling rales	Condensation	–	Yes	Dead/*Klebsiella oxytoca* sepsis.
12	3	F	ALL B	IR	CMR 02-16	20	Fever, cough, headache, irritability, cramps, condensation syndrome	Condensation	4	–	Alive/hepatosplenic candidiasis
13	7	M	ALL B	R/R	Palliative chemotherapy	8	Cough, respiratory distress, drowsiness, diarrhea, cracking rales	Groundglass	–	–	Dead/second relapse to bone marrow, liver failure and cholestasis
14	8	M	ALL B	IR	CMR 02-16	24	Fever, cough, respiratory distress, condensation syndrome	Groundglass	–	yes	Dead/Bloom syndrome
15	2	F	AML	IR	CMR 09-14	25	Fever	Normal	–	–	Alive/no

Abbreviations: ALL B: Acute lymphoblastic leukemia B-cell.ALL T: Acute lymphoblastic leukemia T-cell. AML: acute myeloid leukemia, C: consolidation chemotherapy, IR: Induction to remission. RIR: re-induction to remission. R/R, relapse/refractory.
Treatment.
Memorial Sloan-Kettering-New York-II protocol. Induction: Cyclophosphamide 1200mg/m2 IV day 0. Daunorrubicin 60mg/m2 day 2,3. Vincristine 1.5mg/m2 IV day 1,8,15,22. Prednisone 60mg/m2 PO day 1–22. IT cytosine arabinoside day 0.
Consolidation: Cytocine arabinoside 3000mg/m2 IV days 1,2,8,9; L-asparaginase 6000U/m2 IM three times per week; Methotrexate day 3 and 10, 150 and 200 mg/m2 IV respectively; Vincristine 1.5 mg/m2 IV day 11 and 18. Prednisone 180mg/m2/day PO day 39–46.
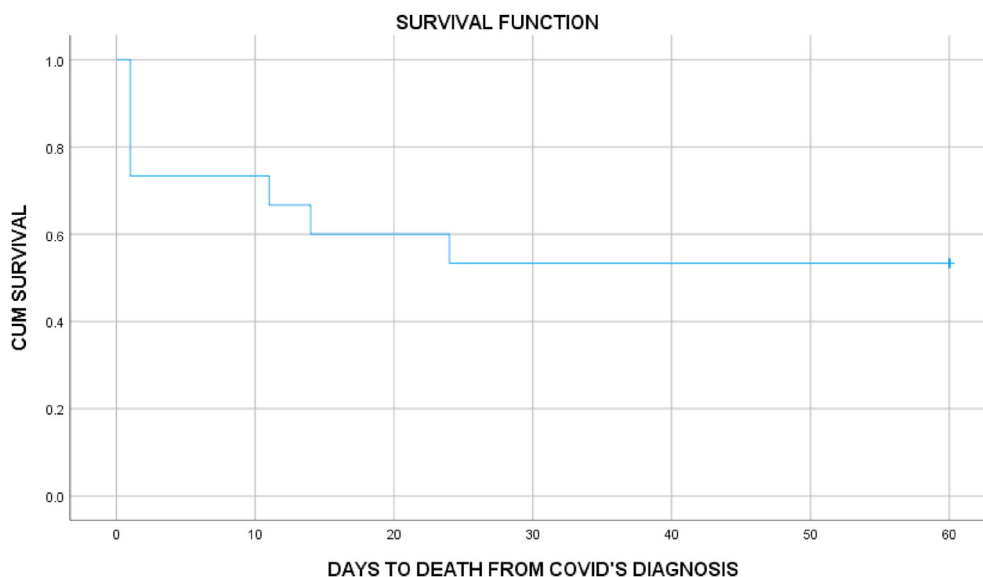**CMR 02–16 protocol:** Prednisone 40mg/m2/day PO, day 0–28, Vincristine 1.5 mg/m2 IV day 0,7,14,21; Daunorrubicin 30 m/m2 IV day 0,1; Methotrexate 4000mg/m2 IV day 2; L-asparaginase 25,000 U IM day 4; IT: Methotrexate, cytosine arabinoside, hydrocortisone day 0, 14, 28.
CMR 14: Cytocine arabinoside 100mg/m2 IV 24 h infusion day 1,2.Cytosine arabinoside 100mg/m2 IV every 12 h days 3–8. Idarubicin 12 mg/m2 IV days 3–5. Etoposide 150 mg/m2 IV days 6–8. IT Cytosine arabinosido and dexamethasone day 0, 15, 28.
Ida-Flag protocol: Fludarabine 30 mg/m2sc PO every 24 h days 1–5; cytosine arabinoside 2000 mg/m2 IV days 1–5; Idarubicin 10 mg/m2 IV days 1,3,5.
Palliative chemotherapy: vincristne 2 mg IV, prednisone 40 mg/m2 PO every 24 h for 5 days, 6-mercaptopurine 50 mg/m2 PO every 24 h for 14 days, methotrexate 30 mg IM weekly.
IT: intrathecal; IV: intravenosus; PO: oral; IM: intramuscular.

B. Sánchez-Jara, A.R. Torres-Jiménez, M.A. Del Campo-Martinez et al.

Pediatric Hematology Oncology Journal 6 (2021) 42—48

SURVIVAL FUNCTION

Graph 1. Survival table.

Table 2
Association of studies of coagulation and liver enzymes with patient outcome.

	Media	p Value
aPTT	Alive 29.9 s (28.5—30.5sec)	0.010
	Deadc35.75 s (30.7—40.9 s)	
D-Dimer	Alive 407 ng/mL (289—562 ng/mL)	0.010
	Dead 4180 ng/mL (582—11183 ng/mL).	
AST	Alive 18.4 U/L (11-34 U/L)	0.035
	Dead162.4 U/L (1.1—813 U/L)	
ALT	Alive 70.8 U/L (6.6—362.3 U/L)	0.041
	Dead 121.2 U/L (20—427 U/L)	

AST: aspartate aminotransferase, ALT: alanine aminotransferase.

(range 6.6—362.3 U/L) and 121.5 U/L (range 20—427U/L, p = 0.041) for those who died. For AST, a mean of 18.4U/L (range 11—34 U/L) for patients who survived and 162.4U/L (1.1—813 U/L) for those who died. (p = 0.03) (Table 2). Ferritin was obtained in 3 patients with a mean of 1794.19 ng/mL. The CRP was determined in 14 of the 15 patients, 13 of which showed an increase in their levels, with a mean of 101 mg/L (range 12.2—261 mg/L). Respiratory distress was documented in 8 patients, of whom 7 died, (p = 0.019 and relative risk of 0.056, 95% CI 0.04—0.789), showing its absence as a protective factor.

Chest radiographs were taken in the 15 patients, 2 were normal, 4 had ground glass image, 6 with ground glass and condensation and 3 only with condensation. Chest CT was performed in 6 children, in all of them the images were in ground glass with bilateral and peripheral distribution, and in the case of the patient with CO-RADS 5, also showing a basal image of crazy paving. It should be noted that only 2 of the patients in whom CT was performed had respiratory distress. Of the 6 patients who had a tomographic report, one died; in which CO-RADS 2 was reported, with the presence of multiple hyperdense images with irregular edges, partially defined, with air bronchogram and distributed bilaterally, with peripheral predominance, those with the largest diameter located in the anterior and posterior segment of the right upper lobe and in the anterior segment of the left upper lobe and left lateral lobe associated with areas of ground glass with thickening in the peri-broncho-vascular interstitium predominantly in the lower segments, thickening of the interlobular septa and nodular reticular pattern of bilateral apical distribution.

Six patients (40%) required oxygen through the nasal cannula, one patient (6.7%) through the venturi mask, and 6 of the 7 patients with respiratory distress required mechanical ventilation. The days from COVID-19 diagnosis to death ranged from 1 to 24, with a follow-up of up to 60 days for survivors (Fig. 1).

4. Discussion

Long-term survival of patients with ALL has increased to 90% with risk-directed therapy and improved supportive care. However, the intensification and prolonged use of chemotherapy drugs are associated with increased risk of infections. Febrile neutropenia is the most common infection-related complication, followed by documented upper respiratory tract infections, ear, bloodstream and gastrointestinal tract [8]. In relation to COVID-19 infection and acute leukemia, few cases have been reported so far, and the clinical course of those that have been described consists of mild to moderately severe respiratory syndrome, although there are anecdotal reports of serious infections and fatal outcomes [9].

In adult patients, inflammation markers and cytokine levels have been established as prognostic factors for severe disease. In pediatric patients, despite systematic reviews of observational studies, it has been difficult to find definitive criteria that can serve as prognostic markers for hospitalization, intensive care requirement, cytokine storm, and progression to respiratory failure or death [10]. Leukocyte abnormalities are usually inconsistent in children; therefore, the white blood cell count does not appear to be a reliable marker of disease severity. In contrast, children with severe COVID-19 show trends consistent with elevated levels of C-reactive protein (CRP), procalcitonin (PCT), and lactic dehydrogenase (LDH) [11]. Regarding the age group, older children have significantly lower lymphocyte counts, CRP, PCT, and elevated creatine kinase compared to those younger than 5 years, however, there is higher mortality in this latter age group [12]. No correlation was found in our analysis between the increase in CRP in association with mortality, which was increased in 13 of our 15 patients. Studies show that there is no higher mortality in children with cancer conditions, chemotherapy and COVID-19, compared to children without cancer [13]. In this group of patients, the parameters of blood cytometry and inflammatory markers will hardly be reliable as predictors of severity; we base this on the fact that the

hemato-oncological patient are already undergoing alterations in the count of their blood cells, both due to their underlying condition and also due to the chemotherapy administered, as well as the high frequency of bacterial, viral and fungal infections that generate a pro-inflammatory state concomitantly or even preceding COVID 19 infection, which makes clinical suspicion difficult and delays the diagnosis of COVID-19 with an impact on mortality in this group of patients. Other biomarkers that can help in the prognosis of COVID-19 are the levels of interleukin 6 (IL-6) and serum ferritin, referred in the cytokine storm in adults, however, they are not available in many hospital centers.

England J.T. et al. Reported the elevation of IL-6 in patients with COVID-19 in 37.5% of severe cases in pediatric age. Studies in adults define factors for severe COVID-19 a ferritin> 1000 ng/mL and CRP> 100 mg/L, but these values will have to be validated in future pediatric studies. It was difficult to define the patients who underwent cytokine storm in our report, due to the little disposition of samples and because there is no agreed definition in children; furthermore, not all cancer patients with severe infection develop a dysregulated immune response and cytokine release as occurs in patients without these conditions, a situation that has not been defined in patients with immunosuppression [14]. Our study was limited to assess procalcitonin and ferritin levels as inflammatory markers associated with mortality, due to the rapid evolution of children who died from COVID-19. At the time of diagnosis of SARS-CoV2 virus infection, 13 of the 15 children had fever associated with neutropenia. Febrile neutropenia (FN) is the most common and life-threatening complication in patients undergoing chemotherapy [15]. SARS-CoV-2 infection appears to be less aggressive in children; even in those with cancer. In our report, the immunosuppression status of patients does not seem to have a significant relationship with mortality caused by SARS-CoV2 infection. Although there are a small number of case reports in children with oncohematologic conditions, these have been shown to be mild to moderate clinical courses [16].

In the coagulation studies of our group of patients, statistical significance was found between the prolongation of aPTT and the increase of D-dimer in the children who died (Table 2). In a meta-analysis performed by Bao J. et al., the prothrombin time (PT) was prolonged in 22.65% of the patients (53/234) and it was shortened in 10.68% (25/234), while the aPTT was prolonged in 21.79% (51/234) and shortened in 5.56% (13/234) of the patients [17]. In other studies, between 20 and 55% of patients hospitalized for SARS-CoV-2 infection presented evidence of coagulation abnormalities, the most important being disseminated intravascular coagulation (DIC) predominantly prothrombotic; with a 25% incidence of deep vein thrombosis [18]. In a large reported series published to date, patients with the worst prognosis have showed much higher D-dimer levels than those with mild disease. In a series of patients without cancer disease, a D-dimer value at admission greater than 1000 ng/mL was one of the main poor prognostic factor. Prolonged PT has also been observed in the most severe patients in these studies [19]. In a study of 183 patients, D-dimer values up to 3.5 times higher were described among patients who died as a result of COVID-19 (median 2120 ng/mL; interquartile range (IQR 0.77—5.27 mg/L) vs. 600 ng/mL (IQR: 0.35—1.29 mg/L; P < 0.001). Patients who died also showed higher levels of fibrin degradation products (median 7.6 mg/L; IQR: 4.0—23.4 mg/L vs. 4.0 mg/L; IQR: 4.0—4.3 mg/L; P < 0.001), and a higher PT (median 15.5 s; IQR: 14.4—16.3 s vs. 13.6 s; IQR: 13.0—14.3 s; P < 0.001) [20,21]. A direct correlation was observed in our patients with the increase in D-dimer and death, so that, as in the mentioned publications, the high D-dimer can be considered a poor prognostic factor since it announces progress to DIC.

Therefore, it is pertinent to measure coagulation parameters, including D-dimer, in children hospitalized with COVID-19, at diagnosis and every 24 h, since those children who increase the value of D-dimer 3 to 4 times above their baseline they could be candidates for treatment in the intensive care unit.

In an early phase of the disease, liver enzymes can be increased in up to 22% of cases, being considered a criterion of severity [22—25]. Lactic dehydrogenase (LDH) levels, AST/ALT ratio, and bilirubin levels could be identified as predictors for early recognition of liver injury and risk of death for COVID-19 patients [16], which corresponds to the findings in our series on AST and ALT (Table 2), however there are other series where AST, ALT and bilirubin did not have a significant difference, unlike hypoalbuminemia where a correlation with severity of the illness [26].

The findings on chest CT scans in 6 of our patients were consistent with what was found in various studies, where ground glass images of a subpleural and bilateral location, are reported more frequently, however, it was not correlated with the severity of COVID. Ludvigsson et al. reported that ground glass opacity was observed in a third of 171 children diagnosed with COVID-19, with local or bilateral irregular shadows in 18.7% and 12.3%, respectively. Overall, 15.8% of children had no symptoms of infection or radiological features of pneumonia. A clinical diagnosis of pneumonia was made in 64.9% of the children [27]. Wu et al. report chest CT images of 80 patients, 76 (95%) had abnormalities indicating pneumonia. The main CT abnormalities observed were ground glass images (73/80 cases, 91%), consolidation (50/80 cases, 63%) and thickening of the interlobular septa (47/80, 59%) [28]. As reported by Shina et al. the most common abnormality is the ground glass image and it is located in the subpleural regions and in the lower lobes [29].

Of our 15 patients diagnosed with acute leukemia and COVID-19 infection, 7 died (46.6%). Six of them initially had respiratory distress that required mechanical ventilation. One patient died of rapid progression of respiratory failure; Due to being in palliative treatment, he was not intubated, receiving only supportive management. This high percentage of mortality is probably secondary to the underlying onco-hematological condition, as well as to the chemotherapy treatment administered. To date, there are 2 theories of the origin of severe lung damage in patients with COVID: the first is secondary to thrombotic complications due to the presence of ACE-2 in the vascular endothelium and to the association of severe disease with elevated levels of D-dimer, which produces endothelial injury and microangiopathy, and the second because a specific adaptive immune response is required to eliminate the SARS-CoV-2 virus, but, in cancer patients, the required immune response is affected [30]. Persistent cytokine release (probably mediated by leukocytes other than T lymphocytes) can cause significant lung damage. In addition to this damage, there is tissue injury and progression to severe disease, especially in ACE2-rich tissues, eg, lung, intestine, and kidneys [31]. Data from China so far has shown that cancer patients infected with COVID-19 have a 3.5-fold increased risk of requiring mechanical ventilation or admission to the intensive care unit, compared to the general population, at the (mortality rate of 28.6%, vs 2.3% for patients with COVID-19 without cancer). In the article by Liang et al. cancer was associated with an increased risk of serious events (admission to the intensive care unit, invasive ventilation or death in 7 of 18 patients 39%, with cancer compared to 124 of 1572 patients 8%, without cancer, p = 0.0003) [32]. The clinical and laboratory data associated with a fatal outcome in our series were: respiratory distress, an increase in D-dimer, prolongation of aPTT, an increase in AST and ALT, as well as the need for mechanical ventilation, resulting in severe systemic damage probably associated with endothelial damage and coagulopathy secondary to SARS-COV2, this coinciding with that reported by Liang.

In the Bouland et al. report, 20 children were identified with cancer and COVID-19. Only 1 patient required non-critical care hospitalization for COVID-19 symptoms. Three other patients without significant COVID-19 symptoms were admitted for concomitant fever and neutropenia, cancer morbidity, or planned chemotherapy. All other pediatric patients had mild symptoms and were treated at home. No patient died [33]. In this study, the detection of SARS-CoV 2 virus infection in the patients was made by RT-PCR as part of the screening prior to admission to receive scheduled chemotherapy or for presenting symptoms suggestive of COVID-19, so they had no recent diagnosis of neoplasia nor had they received intensive chemotherapy, which may condition a more favorable course of the infection, unlike our patients, who 12 were in induction or re-induction to remission and one in consolidation, conditioning this in addition to myelosuppression, other morbidities that could aggravate their condition of health.

In the report by Rojas et al. epidemiological data are provided and the most relevant clinical characteristics and results are described. Fifteen pediatric oncology patients (0—18 years) with proven COVID-19 infection in Madrid up to April 15, 2020 were identified and included. The median age was 10.6 years (range 0.6—18.6). Cancer types included hematologic neoplasms (73%) and solid tumors (27%). Four patients (27%) had received a hematopoietic stem cell transplant (median interval to COVID-19 infection: 209 days, range 113—749). The majority of patients (60%) had received chemotherapy in the 15 days prior to COVID-19 infection. Chemotherapy had to be stopped or delayed in six (40%). Seven (47%) patients were hospitalized due to COVID-19 infection, four (27%) were already hospitalized (nosocomial infection), and four (27%) were seen in the outpatient clinic. The most frequent symptoms were fever (67%) and cough (40%). Two patients were asymptomatic. Chest radiographs were performed in the majority of patients (93%), with pathological findings in 57%. Noteworthy laboratory findings included median white blood cell count at diagnosis of 3195 (range 90—10 690), median lymphocyte count of 580 (range 0—6310), and median D-dimer 291 ng/mL (range 0.7—2620). Two patients required oxygen therapy (nasal cannula, <2 LPM), one of them still required support. All the patients presented favorable clinical results so far, although four of them remained hospitalized. The median hospital stay for infection was 8 days (range 3—26) [34]. Comparing the clinical characteristics with our patients, 86% of them showed alterations in the chest x-ray and 40% required mechanical ventilation. The leukocyte and lymphocyte count is similar in both groups and a relevant result is the D-dimer, which has a mean of 4180 ng/dL in the children of our cohort who died.

Ferrari et al. identified 21 children with cancer and COVID-19 infection, with a median age of 6 years (range 1—17). The tumor types of the 21 positive cases were as follows: 10 leukemias, five bone or soft tissue sarcomas, two lymphomas, two hepatoblastomas, one central nervous system tumor, and one colon carcinoma. Fifteen of these patients were in treatment and six had completed their treatment and were under follow-up. Two patients experienced complications from the viral disease: one, with a diffuse intrinsic pontine glioma and existing respiratory neurological abnormalities, developed pneumonia requiring internal ventilation; another, with Hodgkin lymphoma, who had previously received radiation therapy, developed atypical bilateral pneumonia with mild symptoms. No patient died [35].

Very little data is available on the result COVID-19 in children with blood and cancer disorders. Most children have a mild course and mostly recover.

In our group of patients there was a high mortality, which we have attributed to the following situations: At the time of documenting the SARS-CoV2 virus infection, a treatment with prophylactic/therapeutic anticoagulation had not yet been established in pediatric patients, which could be related to the serious evolution and death, but we must take into account the characteristics of each patient who died, as were the tumor lysis syndrome, evolution to sepsis and acute leukemia refractory to treatment, among others (Table 1.).

5. Conclusions

In this series, we did not find an association between the parameters of blood cytometry in patients with acute leukemia and COVID-19 infection, to establish the diagnostic suspicion and clinical evolution, as well as the risk of death. We observed a statistically significant correlation with the outcome in patients who presented with prolongation of aPTT and an increase in D-dimer, elevation of liver enzymes (AST and ALT), those who had severe respiratory distress and required mechanical ventilation. 93.3% of the patients showed an increase in CRP and only in 3 of them it was possible to measure ferritin, which was found to be elevated. Fever and neutropenia were not shown to predispose a pediatric oncology patient to a fatal outcome. All the children had changes in the chest radiograph, the most consistent image being documented on ground glass. Computed tomography images in 6 patients revealed varying degrees of lung involvement, with the most frequent being ground glass, bilateral and peripheral, with the CORADS classification not correlating with the risk of death.

Due to the clinical characteristics of the patients who died, we concluded that the death was related to complications such as sepsis, one patient with tumor lysis syndrome, another with complicated appendicitis, and in the case of the two patients on palliative chemotherapy for acute leukemia in activity, with COVID-19 infection being a complication that contributed to morbidity and mortality.

This is a small retrospective analysis, which gives us an overview of the evolution of pediatric patients diagnosed with acute leukemia and COVID-19, however, more prospective studies are needed with monitoring of procalcitonin and Interleukin-6 levels, that can help in the diagnosis and prognosis of COVID-19 and therefore make therapeutic decisions in a timely manner.

Declaration of competing interest

There are no prior publications or submissions with any overlapping information, including studies and patients.

This manuscript has not been and will not be submitted to any other journal while it is under consideration.

There are no conflict of interest of the authors.

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