Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The impact of lockdown during the COVID-19 pandemic on newly acute myeloid leukemia patients: Single-centre comparative study between 2019 and 2020 cohorts in Madrid

Dear Editor,

Spain – and specially Madrid – is one of the worst affected countries worldwide by the novel coronavirus disease 2019 (COVID-19) pandemic. A nationwide lockdown was introduced across Spain from March 14 to June 21, 2020 in an attempt to flatten the curve of SARS-CoV-2 infection and reduce the potential impact on the health care system. As reported in other countries [1,2], during the lockdown period there was a cessation or decrease in most non-COVID-19 health services, potentially affecting patients who require prompt access to medical attention, such as those with cancer. This scenario might be worse in rapid progressive entities such as acute myeloid leukemia (AML). The collateral damage of COVID-19 pandemic has scarcely been reported in patients with AML [3]. The impact on outcomes in this group could be related with diagnosis delay, progression due to antineoplastic therapy discontinuation or other reasons. Furthermore, patients with haematological malignancies and COVID-19 present a higher risk of severe events and death [4–6], being AML one of the neoplasms with higher mortality rate [5–8].

Most AML cases present with clinical manifestations, such as mild bleeding or those related to anaemia. Some patients debut with life-threatening conditions secondary to hyperleukocytosis. The time from diagnosis to the initiation of frontline therapy (TDT) has been studied in different series as a potential outcome predictor [9–11]. Nevertheless, the time from clinical onset of AML to the initiation of treatment has hardly been studied.

A retrospective single-centre study in Madrid was conducted, including patients with newly diagnosed AML from the Spanish lockdown initiation to two months after its end (March 14 to August 21, 2020 – five-month period –). This group (2020 cohort) was compared with the 2019 cohort of patients diagnosed with AML during the same period (March 14 to August 21, 2019). Only adults over 18 years-old were included. Patients with initial diagnosis in other centers and later referred to our institution were not included. AML diagnosis was made according to the WHO2016 criteria [12]. Acute promyelocytic leukemia (APL) cases were not excluded. The date of AML diagnosis was established as the first day when a percentage of blasts greater than 20 % was demonstrated in peripheral blood or bone marrow. All patients were included independently of the AML intention-to-treat at diagnosis: intensive therapy candidates, non-intensive therapy candidates and palliative care approach. AML individualized treatment was chosen according to current guidelines [13,14]. The date of AML onset was considered as the first day in which patients referred symptoms related to the disease or the first visit to their general practitioner or the emergency room. Only the visits to the general practitioner/emergency room were taken into account to calculate the number of visits previous to the AML diagnosis. Clinical data was obtained from electronic medical records.

Statistical analysis was performed on IBM SPSS Statistics 22.0 (IBM Corp. in Armonk, NY). A complete descriptive analysis and comparison between groups was carried out (Table SI). The follow-up of the series ended one month after the last date of the inclusion period (September 21, 2019 and September 21, 2020 for each cohort respectively). Survival outcome was analyzed according to Kaplan–Meier estimator. Overall survival (OS) was defined as the time from AML diagnosis to death by any cause or to the last follow-up. Cox proportional-hazards models were constructed based on univariate and multivariate analysis results.

A complete description of demographics, AML biology, clinical and laboratory presentation, first line treatment, and outcomes is presented in Table 1 for both 2019 (n = 14) and 2020 (n = 12) cohorts. No variable demonstrated statistically significant difference between groups. The 2020 cohort presented a higher median leukocyte count in peripheral blood at diagnosis (Fig. 1A), lower median haemoglobin level (Fig. 1B), and similar median platelet count (Fig. 1C) than the 2019 group. The median time from AML symptomatic onset to the first visit to any non-haematologist practitioner was 5 (0–85) days in 2019 group and 10 (0–61) days in 2020 group (Fig. 1D), and the median time from first visit to AML diagnosis was 6 (0–94) days in 2019 and 13 (2–135) days in 2020 (Fig. 1E). The median days from AML onset to diagnosis was 20 (0–96) in the 2019 cohort and 29 (14–145) in the 2020 cohort (Fig. 1F). The median number of visits before AML diagnosis was 0 (0–4) in the 2019 cohort and 2 (0–4) in the 2020 cohort (Fig. 1G). One patient in the 2019 group and two patients in the 2020 group who were planned to receive therapy did not initiate it due to early death secondary to AML complications. TDT was similar in both groups: median of 7 (0–53) days in 2019 and 4 (0–40) days in 2020 ($P = 0.9$), with similar proportion of TDT >15 days (27.3 % in 2019 cohort and 22.2 % in 2020 cohort, $P = 0.9$).

Four patients of the 2020 cohort suffered COVID-19. Real-time polymerase chain reaction (RT-PCR) of nasopharyngeal swab demonstrated SARS-CoV-2 infection in three of them, the remaining patient who tested negative was considered as COVID-19 based on highly epidemiological, clinical and radiological suspicion. All cases developed acute respiratory distress syndrome and 3/4 died because of that reason. Three patients presented with concurrent COVID-19 and AML at AML diagnosis. Of those, one was a 92-year-old Caucasian female not considered to receive anti-tumoural treatment who underwent palliative care. The other two patients were Caucasian mild-age males intensive-therapy candidates with positive SARS-CoV-2 PCR, one of them passed away during first induction therapy and the other one survived. The last patient was an 86-year-old Caucasian female who underwent COVID-19 while receiving second a Azacytidine cycle and died four days after positive SARS-CoV-2 PCR.

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Table 1
Characteristics of AML patients: 2019 cohort and 2020 cohort.

Variables		2019 cohort (N = 14)	2020 cohort (N = 12)
Demographics and AML bioloby			
Age, years	Median (range)	55 (26–90)	63 (45–92)
	≥60, n (%)	6 (42.9)	7 (58.3)
Gender, n (%)	Male	9 (64.3)	7 (58.3)
	Female	5 (35.7)	5 (41.7)
Ethnics, n (%)	Caucasian	11 (78.6)	10 (83.3)
	South-American	3 (21.4)	2 (16.7)
ELN-2017 risk stratification, n(%)	Favourable	4/11 (36.4)	3/10 (30.0)
	Intermediate	4/11 (36.4)	5/10 (50.0)
	Adverse	3/11 (27.3)	2/10 (20.0)
APL, n (%)	No	12 (85.7)	11 (91.7)
	Yes	2 (14.3)	1 (8.3)
Secondary AML, n (%)	Previous haematological malignancy[†]	2 (14.3)	3 (25.0)
	Therapy-related	2 (14.3)	1 (8.3)
Frontline therapy candidate, n (%)	Intensive therapy candidate	10 (71.4)	8 (66.7)
	Non-intensive therapy candidate	2 (14.3)	4 (33.3)
	Palliative care	2 (14.3)	1 (8.3)
Clinical and laboratory presentation of AML at diagnosis			
ECOG performance status, *n (%)*	ECOG <2	13 (92.9)	8 (66.7)
	ECOG ≥2	1 (7.1)	4 (33.3)
Symptoms, *n (%)*	Asymptomatic	1 (7.1)	0 (0)
	Weakness	10/13 (76.9)	11 (91.7)
	Weight loss	4/13 (30.8)	2 (16.7)
	Bleeding[‡]	2/13 (15.4)	6 (50.0)
	Fever	3/13 (23.1)	3 (25.0)
	Profuse sweating	4/13 (30.8)	2 (16.7)
	Skin lesions	1/13 (7.1)	2 (16.7)
	Gastrointestinal	0/13 (0)	4 (33.3)
	Neurological[§]	4/13 (30.8)	1 (8.3)
	Respiratory	1/13 (7.1)	2 (16.7)
	Mass	2/13 (15.4)	1 (8.3)
	Other	1/13 (7.1)	4 (33.3)
Infection, *n (%)*	No	9 (64.3)	9 (75)
	Yes	5 (35.7)	3 (25.0)
Leukostasis, *n (%)*	No	13 (92.9)	10 (83.3)
	Yes	1 (7.1)	2 (16.7)
Leucocyte count, $x10^9$/l	Median (range)	5.1 (0.9–391)	26 (1.6–451)
Blast count [N], $x10^9$/l	Median (range)	0.3 (0–391)	13.8 (0–451)
Hyperleukocytosis, *n (%)*	Over 100 × 10^9/l	2 (14.3)	2 (16.7)
	Over 200 × 10^9/l	2 (14.3)	2 (16.7)
Haemoglobin level, g/l	Median (range)	92 (54–123)	83 (54–137)
Platelet count, $x10^9$/l	Median (range)	50 (0.7–340)	53 (22–420)
Lactate dehydrogenase level, U/l	Median (range)	349 (169–1,717)	438 (142–3,708)
Coagulopathy, *n (%)*	No	11 (78.6)	6 (50.0)
	Yes	3 (21.4)	6 (50.0)
AML first line treatment and outcomes			
ICU admission at diagnosis, *n (%)*	No	10/12 (83.3)	9/11 (81.2)
	Yes	2/12 (16.7)	2/11 (18.2)
Cytorreduction at diagnosis, *n (%)*	Leukapheresis	2/12 (16.7)	2/11 (18.2)
	Hydroxyurea	1/12 (8.3)	0/11 (0)
No treatment initiated	*n (%)*	1/12 (8.3)	2/11 (18.2)
Clinical trial inclusion, *n (%)*	No	7/11 (63.4)	6/9 (66.7)
	Yes	4/11 (36.4)	3/9 (33.9)
Therapy dose adjustement, *n (%)*	No	9/11 (81.2)	8/9 (88.9)
	Yes	2/11 (18.2)	1/9 (11.1)
Frontline response, *n (%)*[⁑]	CR MRD- by FC	4/9 (44.4)	4/6 (66.7)
	CR MRD + by FC	3/9 (33.3)	2/6 (33.3)
	RD/Progression	2/9 (22.2)	0 (0)
Status, *n (%)*	Alive	12 (85.7)	7 (58.3)
	Death	2 (14.3)	5 (41.7)

AML, acute myeloblastic leukemia; APL, acute promyelocytic leukmiea; CR, complete remission; ECOG, Eastern Cooperative Oncology Group Performance Status; ELN, European Leukemia Net; FC, flow cytometry; ICU, intensive care unit; MRD, minimal residual disease; RD, refractory disease.

[†] 2019 cohort: History of myelodysplastic syndrome in two patients. 2020 cohort: History of chronic myelomonocytic leukemia in two patients and blastic phase of polycythaemia vera in one patient.

[‡] All patients presented with mild to moderate bleeding except from one patient in 2020 cohort who presented with major bleeding at a critical site (intracranial).

[§] All patients presented with mild neurological symptoms except from one patient in each cohort who presented with coma.

[N] According to leucocyte count blood smear blast percentage count performed by two specialists.

[⁑] Including only intensive therapy patients. No patient candidate to non-intensive therapy had AML response evaluated during the study period.

The median follow-up of the 2019 and 2020 cohorts was 75 (13–192) days and 63 (1–174) days, respectively. At the end of follow-up period 2/14 and 5/12 patients died in 2019 and 2020 groups, respectively ($P = 0.2$). Overall survival by Kaplan-Meier estimator for 2019 and 2020 AML groups is presented in Fig. 1H. In Figure S1 OS Kaplan-Meier curves according to 2019, 2020 non−COVID-19 and 2020 COVID-19 groups are presented. A complete univariate analysis of OS in the whole series was performed (Table SII). The next variables were associated with lower OS, although only ECOG PS demonstrated statistical significance: 2020 cohort, age ≥60 years-old, visits previous to AML diagnosis ≥2, ECOG PS ≥ 2 at AML diagnosis, COVID-19 undergoing, time from onset to AML diagnosis >15 days, and TDT > 15 days. No variable included in multivariable analysis was independently associated with OS.

Here is presented the first report regarding the impact of COVID-19 pandemic lockdown on newly AML patients. Patients diagnosed with AML during the first months of COVID-19 pandemic in Spain presented with worse performance status defined by ECOG and with a higher proportion of bleeding when comparing with AML patients diagnosed during the same period in 2019. AML patients diagnosed along the lockdown period and up to two months later presented with higher leukocyte count, lower haemoglobin level, and higher LDH level. All those findings could be related to a delay in medical attention or a later AML diagnosis during COVID-19 pandemic, as reported in this article. Waiting a short period of time at AML diagnosis in order to perform a better characterization of the disease to choose the best available therapeutic regimen appears to be a safe approach in clinically stable patients who finally receive intensive therapy [10,11]. This strategy is particularly important in the era of novel agents. TDT did not differ between 2019 and 2020 patients in our series, nor the rate of inclusion into clinical trials. Nevertheless, it appears that the time of evolution before AML diagnosis plays a role in the presentation of the disease and in short term survival, which should be taken into account when designing the frontline therapy. The longer evolution previous to AML diagnosis in the 2020 cohort was probably related to the nationwide Spanish lockdown and to a longer time to request for medical attention. COVID-19 pandemic lockdowns could lead to a delay of presentation and a potential poorer outcome on newly AML cases. It is possible that some patients will not initiate frontline therapy due to a prompt death or AML complications during COVID-19 pandemic. Furthermore, newly diagnosed AML patients who underwent SARS-CoV-2 infection presented a fateful prognosis that contributed to a worse outcome of the 2020 cohort.

To conclude, patients with AML are suffering direct and indirect effects of COVID-19, which could be reflected in changes on the history of the disease and worse outcomes. Further efforts should be taken to avoid delays in diagnosis and treatment in patients with AML and other haematological neoplasms, and to carry out prevention strategies in this group of vulnerable patients.

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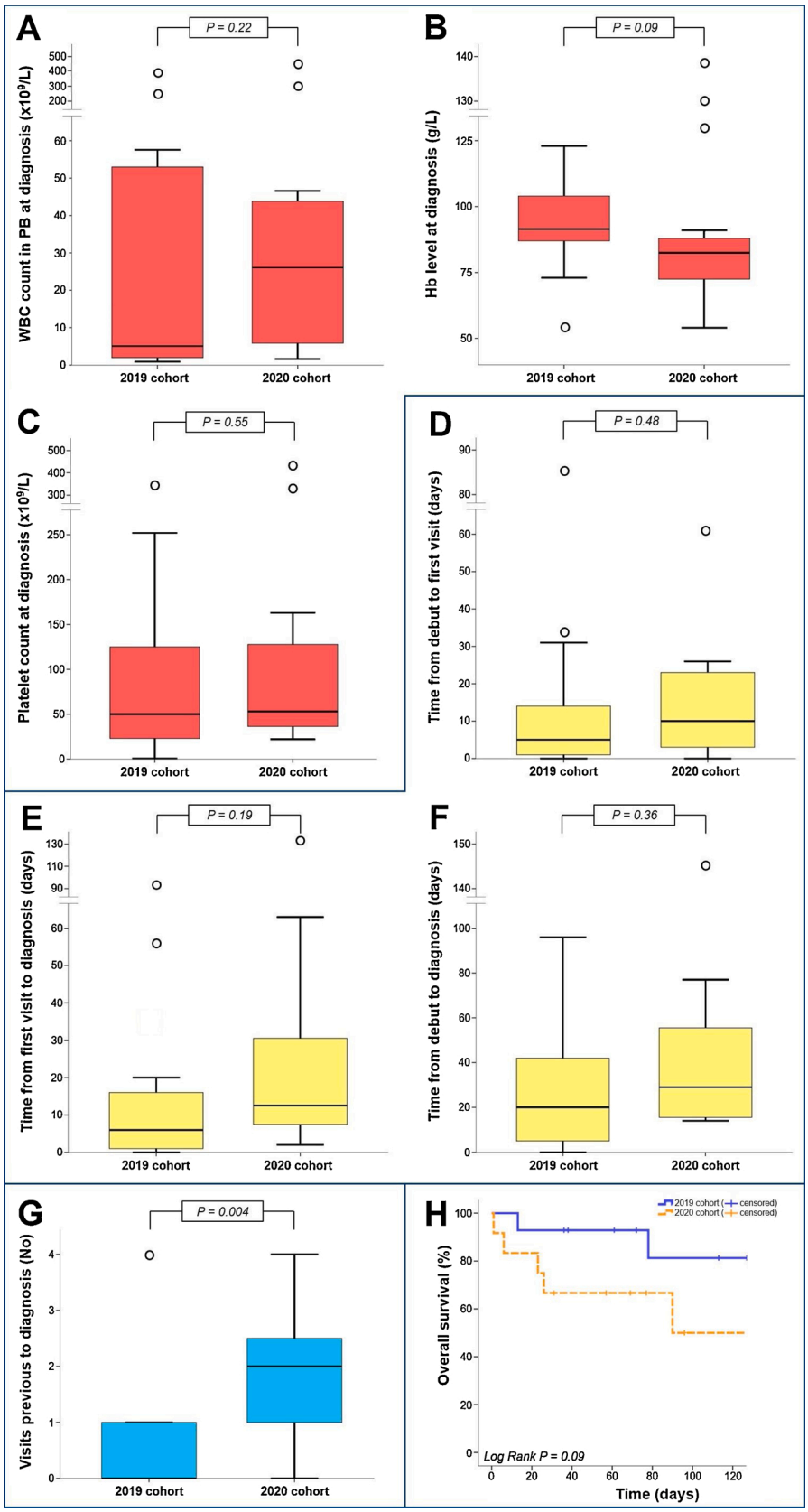

Fig. 1. Laboratory findings in peripheral blood at AML diagnosis, clinical evolution previous to AML diagnosis, and overall survival estimation according to 2019 cohort and 2020 cohort. *P* values refer to comparison between 2019 cohort and 2020 cohort. (A) White blood cell count, (B) haemoglobin level, and (C) platelet count at AML diagnosis. (D) Time from AML symptoms onset to first visit to general practitioner or emergency room, (E) time from first visit to general practitioner or emergency room to AML diagnosis, and (F) time from AML symptoms onset to diagnosis. (G) Number of visits to general practitioner or emergency room previous to AML diagnosis since the beginning of symptoms related to the disease. (H) Overall survival by Kaplan-Meier estimator in patients with AML according to 2019 cohort and 2020 cohort.

Authors contributions

FM, CN, JL and PH conceived of, and designed the study. FM, CN, LP, CJ, and JM contributed to data acquiring, data analysis, or data interpretation. FM, CN and JM wrote the manuscript. LP, CJ, JL and PH were involved in critical revision of the report. All authors reviewed and approved the final version. All authors were involved in patients care.

Ethics approval

The study was approved by the Clinical Research Ethics Committee, Ramón y Cajal University Hospital in Madrid, Spain (130-20 and 141-2020).

Declaration of Competing Interest

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2021.106518.

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