COVID-19 in adult acute myeloid leukemia patients: a long-term follow-up study from the European Hematology Association survey (EPICOVIDEHA)

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Abstract

Patients with acute myeloid leukemia (AML) are at high risk of mortality from coronavirus disease 2019 (COVID-19). The optimal management of AML patients with COVID-19 has not been established. Our multicenter study included 388 adult AML patients with COVID-19 diagnosis between February 2020 and October 2021. The vast majority were receiving or had received AML treatment in the prior 3 months. COVID-19 was severe in 41.2% and critical in 21.1% of cases. The chemotherapeutic schedule was modified in 174 patients (44.8%), delayed in 68 and permanently discontinued in 106. After a median follow-up of 325 days, 180 patients (46.4%) had died. Death was attributed to COVID-19 (43.3%), AML (26.1%) or to a combination of both (26.7%). Active disease, older age, and treatment discontinuation were associated with death, whereas AML treatment delay was protective. Seventy-nine patients had a simultaneous AML and COVID-19 diagnosis, with an improved survival when AML treatment could be delayed. Patients with COVID-19 diagnosis between January and August 2020 had a significantly lower survival. COVID-19 in AML patients was associated with a high mortality rate and modifications of therapeutic algorithms. The best approach to improve survival was to delay AML treatment.

Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy often requiring immediate chemotherapeutic treatment due to high risk of early disease-related life-threatening complications including death [1]. AML patients are severely immunocompromised, and infections are frequently associated with both, the disease-related weakened immunity and the aggressive chemotherapeutic regimen [2]. Despite a lower relevance as compared to bacterial and fungal infections, respiratory viruses may also affect AML patients, particularly during seasonal epidemics [3].

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with a severe clinical presentation in AML patients. Most of the studies performed in the pre-vaccine era reported mortality rates higher than 40% [4–8]. The literature regarding COVID-19 in AML patients is limited to small cohorts [9–10], case reports and case series [10–14], expert opinions and consensus, [13, 15] or series reporting both patients with AML and acute lymphoblastic leukemia [16–17]. Therefore, specific data on large patient cohorts with long-term follow-up are still lacking. To the best of our knowledge, there are still no evidence-based algorithms guiding clinicians to choose the best therapeutic approach and timing, particularly in patients with a simultaneous diagnosis of AML and COVID-19 diagnosis.

Thus, in order to establish the best therapeutic approach, we aimed to describe clinical features and long-term follow-up of a large cohort of AML patients with COVID-19 registered in the EPICOVIDEHA registry, with a particular focus on patients with a concomitant diagnosis of AML and COVID-19.

Material And Methods

Study design, patients, and procedures

This is an observational multicenter study of patients with AML who developed COVID-19 between February 2020 and October 2021. Our analysis comprised data from the EPICOVIDEHA (www.clinicaltrials.gov; ID NCT04733729) international open web-based registry for patients with hematological malignancies (HM) and SARS-CoV-2 infections initiated in February 2020 by members of the Scientific Working Group (SWG) Infection in Hematology of the European Hematology Association (EHA). EPICOVIDEHA was approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (ID 3226). Additionally, the respective local ethics committee of each participating institution approved as appropriate. EPICOVIDEHA methodology has been described elsewhere [18]. The electronic case report form (eCRF) is accessible online via www.clinicalsurveys.net (EFS Summer 2021, TIVIAN GmbH, Cologne, Germany) [19]. Each documented patient was reviewed and validated by experts in infectious

diseases and hematology. Inclusion criteria were: a) active AML within the last five years before COVID-19 diagnosis, b) adult patients ≥ 18 years old, and c) laboratory-based diagnosis of SARS-CoV-2 infection. Data on patient baseline conditions pre-COVID-19 (i.e., age, sex, AML status at COVID-19 diagnosis, comorbidities), AML clinical management (i.e., last chemotherapy strategy, hematopoietic stem-cell transplantation [HSCT], COVID-19 diagnosis and management (i.e., the reason for a diagnostic test, symptoms at onset, hospitalization) and outcome (i.e., mortality, attributable mortality [assessed by the medical team in charge of the patient], last day of follow-up) were also recorded. Additionally, information regarding AML treatment modifications (i.e., delay or discontinuation) due to COVID-19, and the contribution of the diagnosis of COVID-19 in AML relapse or AML status at last day of follow up was also collected. Status of hematological malignancy at COVID-19 onset and last follow up was defined as active (onset, stable disease, refractory/resistant) or controlled (complete response) based on the reports from the respective participating institution. COVID-19 severity was graded according to international standards as previously described [4, 20–21]. Patients were divided in three time periods as follows: a) January 2020 to August 2020, to cover the first global wave of the pandemic; b) September 2020 to February 2021, with the patients diagnosed in the final holiday period of 2020-2021; and c) March 2021 to September 2021, including patients diagnosed after the vaccines became available.

Study objectives

The primary objective of this study was to evaluate the epidemiology and the outcome of AML patients with COVID-19. Secondary objectives were: 1) to estimate the prevalence of disease severity (i.e., asymptomatic, mild, severe disease and ICU admission; 2) to describe the overall case-fatality rate; and 3) to stratify patients according to their treatment phase (induction, consolidation, maintenance, palliative, reinduction), chemotherapeutic program modification due to COVID-19 (treatment discontinuation, delay or continuation), and timing of COVID-19 diagnosis.

Sample size and statistical analysis

No *a priori* sample size calculation was performed for this analysis. Categorical variables were described using frequencies and percentages, whereas continuous variables were expressed as median, interquartile range (IQR) and absolute range. A Cox regression hazard model was designed and run with variables considered to play a role in the mortality of AML patients with COVID-19, as previously described [4]. A multivariable Cox regression model was calculated with the Wald backward method, and only those variables with $p \leq 0.1$ were displayed. Mortality was analyzed using Kaplan-Meier survival plots. Log-rank test was used to compare the survival probability of the patients included in the different models. A p -value ≤ 0.05 was found statistically significant. SPSS v27.0 was employed for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States).

Role of funding source

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Results

Between February 2020 and October 2021, 556 consecutive adult AML patients with confirmed SARS-CoV-2 infection were reported in the EPICOVIDEHA registry, from 132 centres and 20 countries around the world. Out of these patients, 168 (30.2%) were excluded from this analysis due to missing data.

The demographic and clinical characteristics of the remaining 388 patients are shown in Table 1. The median age was 59 years (IQR: 45-70) with a slight male predominance (52.6%). Most patients had at least one underlying comorbidity with chronic cardiopathy (i.e., hypertension, obstructive arteriopathy, atrial fibrillation) being the most frequent, whereas 175

patients (45.1%) had comorbidities. At the time of COVID-19 diagnosis, 196 patients (50.5%) had controlled AML, and 192 (49.5%) had active disease, including 79 (20.4%) patients at AML onset. Only 110 patients (28.3%) were not on active treatment. Overall, 237 patients (64.6%) had received intensive chemotherapy and transplantation, being the most common strategies immediately before COVID-19. The chemotherapeutic program was modified because of COVID-19 in 174 (44.8%) patients; in 106 (60.9%) it was permanently discontinued, whereas in the remaining 68 (39.1%) it was delayed and resumed after a median of 1 month (IQR: 1-2) since COVID-19 diagnosis. At COVID-19 onset, 71 (18.3%) and 53 (13.7%) patients had neutrophil and lymphocyte counts below $0.5 \times 10^9/\text{mm}^3$ and $0.2 \times 10^9/\text{mm}^3$, respectively. Two hundred and twenty patients (56.7%) had pulmonary symptoms at COVID-19 onset, mainly cough and dyspnoea, 82 (21.1%) exhibited only extra-pulmonary symptoms and 86 (22.2%) were asymptomatic and diagnosed with COVID-19 after screening. As shown in Table 1, COVID-19 severity was critical in 82 patients (21.1%), severe in 160 (41.2%), mild in 69 (17.8%), and asymptomatic in the remaining cases (19.6%). Overall, 293 patients (75.5%) were hospitalized during the COVID-19 for a median of 17 days (IQR: 8-30). Eighty-two patients (21.1%) were admitted to an intensive care unit (ICU) for a median stay of 10 days (IQR: 5-20), 63 (76.8%) of whom required invasive mechanical ventilation.

Table 1
Demographic and clinical features of 388 AML patients at COVID-19 diagnosis.

	n	%
Sex		
Female	184	47.4
Male	204	52.6
Age, median (IQR) [range]	59 (45-70) [18-89]	
Comorbidities	213	54.9
Status AML at COVID-19 diagnosis		
Controlled disease	196	50.5
<i>Complete remission</i>	196	50.5
Active disease	192	49.5
<i>Onset</i>	79	20.4
<i>Stable disease</i>	48	12.4
<i>Refractory/Resistant</i>	65	16.8
Last/ongoing treatment strategy before COVID-19		
Treatment	367	94.6
Conventional chemotherapy	250	64.4
<i>Last month</i>	172	44.3
<i>Last three months</i>	46	11.9
<i>> 3 months</i>	32	8.2
HSCT	72	18.6
<i>Last month</i>	8	2.1
<i>Last three months</i>	11	2.8
<i>> 3 months</i>	53	13.7
Supportive measures	45	11.6
<i>Last month</i>	27	7.0
<i>Last three months</i>	9	2.3
<i>> 3 months</i>	4	1.0
<i>Not stated</i>	5	1.3
No treatment	21	5.4
COVID-19 infection		
AML , acute myeloid leukaemia; BAL , bronchioalveolar lavage; COVID-19 , coronavirus disease 2019; HSCT , hematopoietic stem cell transplantation; ICU , intensive care unit; IQR , interquartile range; mm³ , cubic meters		
° Data can be super additive		

	n	%
Critical infection	82	21.1
Severe infection	160	41.2
Mild infection	69	17.8
Asymptomatic	77	19.8
COVID-19 diagnosis		
Swab	376	96.9
BAL+Swab	5	1.3
Serology	4	1.0
BAL	3	0.8
Symptoms at COVID-19 onset		
Pulmonary	144	37.1
Screening	86	22.2
Extrapulmonary	82	21.1
Pulmonary + Extrapulmonary	76	19.6
Neutrophils (x 10⁶/mm³)°		
≤ 0.5	71	18.3
0.501 – 0.999	38	9.8
≥ 1	203	52.3
Lymphocytes (x 10⁶/mm³)°		
≤ 0.2	53	13.7
0.201 – 0.499	56	14.4
≥ 0.5	211	54.4
Stay during COVID-19		
Admitted in hospital	293	75.5
<i>Duration of the stay in hospital, median days (IQR) [range]</i>	17 (8-30) [1-210]	
ICU stay	82	21.1
<i>Duration of the ICU stay, median days (IQR) [range]</i>	10 (5-20) [1-111]	
Invasive mechanical ventilation	63	16.2
Non-invasive mechanical ventilation	19	4.9
At home	117	30.2
AML, acute myeloid leukaemia; BAL, bronchioalveolar lavage; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IQR, interquartile range; mm³, cubic meters		
° Data can be super additive		

	n	%
Outcome		
Alive	208	53.6
<i>Observation time, median days (IQR) [range]</i>	325 (117-386)	[3-639]
Dead	180	46.4
<i>Observation time, median days (IQR) [range]</i>	20 (8-58)	[0-528]
Reason for death [°]		
<i>COVID-19</i>	78	43.3
<i>COVID-19 + Haematological malignancy</i>	48	26.7
<i>Haematological malignancy</i>	47	26.1
<i>Unknown reasons</i>	7	3.9
AML , acute myeloid leukaemia; BAL , bronchioalveolar lavage; COVID-19 , coronavirus disease 2019; HSCT , hematopoietic stem cell transplantation; ICU , intensive care unit; IQR , interquartile range; mm³ , cubic millimeters		
[°] Data can be super additive		

Patients were followed-up for a median of 104 days (IQR: 18-346) since COVID-19 diagnosis; 325 days (IQR: 117-386) in 208 (53.6%) surviving patients versus 20 days (IQR: 8-58) in the 180 (46.4%) patients who died. The reported primary reason for death was COVID-19 in 78 (43.3%) patients, AML in 47 (26.1%), a combination of both in 48 (26.7%) and unknown in 7 patients (3.9%), as shown in Table 1 and Figure 1. The mortality rate of patients with an ongoing or recent (<1 month before COVID-19 diagnosis) AML treatment, so as those treated until 1 to 3 months before COVID-19 diagnosis was significantly higher than those receiving a treatment until 3 months or earlier before COVID-19 ($p<0.001$), as shown in Figure 2. When considering AML patients with the last chemotherapy <1 month before COVID-19 diagnosis, a higher mortality rate was observed in 68 (80.9%) patients who discontinued treatment, regardless of the treatment phase (Figure 3). Furthermore, a significantly lower mortality rate was observed in 49 (18.4%) patients with chemotherapy delay (overall mortality rate: 18.4%, $n=49$), as opposed to those patients with no delay (37.5%, $n=9$) ($p<0.001$), regardless of the treatment phase (Figure 2 and Figure 4). The overall mortality rate of patients in induction (67.1%, $n=51$) or reinduction (77.7%, $n=28$) was higher as compared to those in consolidation (20%, $n=10$) during the last month prior to COVID-19 ($p<0.001$). In the univariable analysis, several factors were associated with an increased mortality (Table 2): older age, previous comorbidities (i.e., chronic cardiopathy or renal impairment), active malignancy, critical COVID-19, or permanent AML treatment discontinuation. On the contrary, having a neutrophil or lymphocyte count above $0.5 \times 10^9/\text{mm}^3$ and $0.2 \times 10^9/\text{mm}^3$, respectively, AML treatment >3 months before COVID-19 diagnosis and AML treatment delay were associated to a reduced mortality. In the multivariable model, active disease (HR: 4.197, $p<0.001$), older age (HR: 1.016, $p=0.012$), and treatment discontinuation (HR: 4.417, $p<0.001$) were associated with a higher mortality, as opposed to treatment delay, which was found to be protective (HR: 0.367, $p=0.027$). After a time-dependent analysis, it was observed that overall survival in patients with COVID-19 diagnosis between January 2020 and August 2020 was significantly lower survival than those who were diagnosed between September 2020 and February 2021 and between March 2021 and September 2021 ($p=0.037$; Figure S2).

Table 2
Overall mortality predictors of death in AML patients with COVID-19.

OVERALL MORTALITY	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
Lower limit	Upper limit	Lower limit	Upper limit					
Sex								
Female	-	-	-	-	-	-	-	-
Male	0.403	1.135	0.844	1.526	-	-	-	-
Age	<0.001	1.029	1.019	1.040	0.012	1.016	1.004	1.028
Comorbidities	0.001	1.699	1.251	2.308	0.437	0.831	0.520	1.326
Malignancy status								
Controlled disease	-	-	-	-	-	-	-	-
Active disease	<0.001	4.353	3.111	6.092	<0.001	4.197	2.196	8.020
COVID-19 infection								
Asymptomatic	-	-	-	-	-	-	-	-
Mild infection	0.370	0.770	0.435	1.363	0.566	0.804	0.382	1.694
Severe infection	0.454	1.187	0.758	1.857	0.812	1.073	0.600	1.920
Critical infection	<0.001	3.624	2.306	5.696	0.249	1.417	0.783	2.565
Neutrophils (x 10⁶/mm³)								
≤ 0.5	-	-	-	-	-	-	-	-
0.501 – 0.999	0.017	0.529	0.314	0.891	0.359	0.761	0.424	1.365
≥ 1	<0.001	0.426	0.299	0.608	0.473	1.198	0.732	1.961
Lymphocytes (x 10⁶/mm³)								
≤ 0.2	-	-	-	-	-	-	-	-
0.201 – 0.499	0.982	1.006	0.624	1.620	0.309	0.702	0.355	1.389
≥ 0.5	0.009	0.581	0.388	0.872	0.144	0.661	0.379	1.152
Last chemotherapy/HSCT								
In the last month	-	-	-	-	-	-	-	-
In the last 3 months	0.464	0.863	0.583	1.279	0.903	1.038	0.568	1.897
Chemotherapy ended > 3 months before COVID-19	<0.001	0.368	0.235	0.577	0.225	2.204	0.614	7.909
Not stated	0.291	0.346	0.048	2.479	0.566	1.916	0.208	17.667

AML, acute myeloid leukemia; **COVID-19**, coronavirus disease 2019; **ICU**, intensive care unit; **HSCT**, hematopoietic stem cell transplantation; **mm³**, cubic meters; **TX**, therapeutic program for AML.

OVERALL MORTALITY	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
Not applicable	0.955	1.018	0.548	1.892	0.819	0.891	0.333	2.386
AML treatment delay								
TX NOT delayed and NOT discontinued	-	-	-	-	-	-	-	-
TX delayed but NOT discontinued	0.013	0.361	0.161	0.808	0.027	0.367	0.151	0.891
TX discontinued	<0.001	4.271	2.372	7.690	<0.001	4.417	2.306	8.460
Relapse after COVID-19								
No	-	-	-	-	-	-	-	-
Yes, due to COVID-19	0.350	0.712	0.350	1.451	-	-	-	-
Yes, NOT due to COVID-19	0.796	0.928	0.527	1.636	-	-	-	-
Unknown	0.182	1.746	0.770	3.958	-	-	-	-
AML , acute myeloid leukemia; COVID-19 , coronavirus disease 2019; ICU , intensive care unit; HSCT , hematopoietic stem cell transplantation; mm³ , cubic meters; TX , therapeutic program for AML.								

Table 3 describes the demographic and clinical features of the 79 patients with a simultaneous AML and COVID-19 diagnosis. In 18 patients (22.8%), COVID-19 was diagnosed before induction start, resulting in a treatment delay. A higher overall survival was observed in patients with treatment delay (Table 3, Figure S1).

Table 3
Demographic and clinical features of 79 AML patients at malignancy onset at COVID-19 diagnosis.

	Overall (<i>n</i> =79)		No treatment before COVID-19 (<i>n</i> =18)		Induction treatment start before COVID-19 (<i>n</i> =61)	
	n	%	n	%	n	%
Sex						
Female	35.0	44.3	10.0	55.6	25.0	41.0
Male	44.0	55.7	8.0	44.4	36.0	59.0
Age , median (IQR) [range]	65 (50-76) [18-88]		66 (55-72) [18-88]		65 (50-76) [19-86]	
Comorbidities	48.0	60.8	11.0	61.1	37.0	60.7
COVID-19 infection						
Critical infection	23.0	29.1	3.0	16.7	20.0	32.8
Severe infection	36.0	45.6	8.0	44.4	28.0	45.9
Mild infection	10.0	12.7	4.0	22.2	6.0	9.8
Asymptomatic	10.0	12.7	3.0	16.7	7.0	11.5
COVID-19 diagnosis						
Swab	76.0	96.2	18.0	100.0	58.0	95.1
BAL+Swab	2.0	2.5	0.0	0.0	2.0	3.3
Serology	1.0	1.3	0.0	0.0	1.0	1.6
Symptoms at COVID-19 onset						
Pulmonary	39.0	49.4	9.0	50.0	30.0	49.2
Extrapulmonary	14.0	17.7	4.0	22.2	10.0	16.4
Pulmonary + Extrapulmonary	13.0	16.5	2.0	11.1	11.0	18.0
Screening	13.0	16.5	3.0	16.7	10.0	16.4
Neutrophils (x 10⁶/mm³)°						
≤ 0.5	24.0	30.4	4.0	22.2	20.0	32.8
0.501 – 0.999	10.0	12.7	2.0	11.1	8.0	13.1
≥ 1	34.0	43.0	9.0	50.0	25.0	41.0
Lymphocytes (x 10⁶/mm³)°						
≤ 0.2	11.0	13.9	1.0	5.6	10.0	16.4
0.201 – 0.499	11.0	13.9	2.0	11.1	9.0	14.8
AML , acute myeloid leukemia; BAL , bronchioalveolar lavage; COVID-19 , coronavirus disease 2019; HSCT , hematopoietic stem cell transplantation; ICU , intensive care unit; IQR , interquartile range; mm³ , cubic meters						
° Data can be super additive						

	Overall (n=79)		No treatment before COVID-19 (n=18)		Induction treatment start before COVID-19 (n=61)	
≥ 0.5	50	63.3	13.0	72.2	37.0	60.7
Stay during COVID-19						
Admitted in hospital	73	92.4	15.0	83.3	58.0	95.1
Duration of the stay in hospital, median days (IQR) [range]	20 (9-32) [2-106]		14 (4-24) [2-86]		22 (9-36) [3-106]	
ICU stay	23	29.1	3.0	16.7	20.0	32.8
Duration of the ICU stay, median days (IQR) [range]	7 (4-12) [1-32]		5 (2-10) [2–10]		7 (4-12) [1-32]	
Invasive mechanical ventilation	18	22.8	1.0	5.6	17.0	27.9
Non-invasive mechanical ventilation	4	5.1	0.0	0.0	4.0	6.6
At home	10	12.7	4.0	22.2	6.0	9.8
Outcome						
Alive	26	32.9	8.0	44.4	18.0	29.5
Observation time, median days (IQR) [range]	266.5 (85-386) [11-613]		266.5 (122-353) [44-613]		277.5 (75-408) [11-601]	
Dead	53	67.1	10.0	55.6	43.0	70.5
Observation time, median days (IQR) [range]	19 (6.5-57) [0-528]		14 (5-48) [0-528]		21 (7-63) [0-331]	
Reason for death°						
COVID-19	20	37.7	3	30.0	17	39.5
COVID-19 + Hematological malignancy	16	30.2	4	40.0	12	27.9
Hematological malignancy	17	32.1	3	30.0	14	32.6
AML, acute myeloid leukemia; BAL, bronchioalveolar lavage; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IQR, interquartile range; mm³, cubit meters						
° Data can be super additive						

Discussion

Currently, there is a gap of knowledge regarding COVID-19 in AML patients, as the current evidence is restricted to small patient cohorts, case reports/series, or expert opinions [9–17]. This gap has resulted in a difficulty to establish the best strategy to manage AML patients during the pandemic [22–23]. Altogether, the current evidence suggests that AML patients often present with a severe clinical form, with frequent respiratory distress and very high mortality rate, between 40 and 50% as compared to the pre-vaccine era. Here we present, to the best of our knowledge, the largest survey on AML patients with COVID-19, with 388 patients reported from 132 institutions, with a special focus on the long-term follow-up. The data presented in our manuscript confirm that AML patients frequently have a severe clinical presentation (41.2%) of COVID-19, mainly with respiratory symptoms, and a high rate of ICU admission (21.1%).

Neutrophil and lymphocyte counts were not found to be significantly associated with mortality in our multivariable model. The potential role of neutropenia as a risk factor for death in AML is of particular relevance considering that neutrophil function impairment is a typical feature of this malignancy. There are many studies addressing neutropenia as a potential risk factor in COVID-19, but only four of them were able to support its role as a factor affecting survival [24–27]. In particular, a recent study from the Memorial Sloan Kettering Cancer Center (New York, NY, USA), showed that neutropenia between the seven days immediately prior to and up to 28 days after SARS-CoV-2 diagnosis, was associated with increased odds of death [27]. In our study, severe neutropenia was found to be significantly associated with the risk of death at univariable analysis, however, this association was lost in the multivariable model, suggesting that severe neutropenia may not be associated with death in AML patients developing COVID-19.

In our study, we tried to establish the best therapeutic strategy for AML patients with COVID-19. So far, the best therapeutic option for these patients and timing for treatment initiation was only based on expert opinions and consensus [22–23], given the lack of evidence-based algorithms to guide clinicians. This is particularly relevant for naïve AML patients with a concomitant symptomatic SARS-CoV-2 infection. The general recommendation for these patients has been to postpone all treatments not requiring urgent initiation, including a limitation of cytoreductive therapies if needed [22]. Although the current dogma of considering AML a medical urgency is changing, as suggested by some recent studies [28], prompt treatment start is often recommended in routine practice, especially in patients with de novo or with relapsed/refractory disease. Our data suggest that delayed treatment is the best therapeutic option for AML patients with COVID-19, as shown by a lower death rate when treatment was postponed. Similar data were also shown by a Spanish group [9]: in their patient cohort of 108 patients, a lower mortality rate was observed in patients with delayed chemotherapy as compared with those with or without treatment modification. However, those results were observed only in the univariable analysis. Our multivariable model confirmed that a chemotherapeutic program delay was associated with a reduced death rate, having a significant protective role (HR: 0.367; $p=0.027$). Interestingly, even when focusing on patients with new onset AML and COVID-19, we found a better overall survival in those patients in which AML induction delay was possible. The negative impact of AML treatment discontinuation on the observed death rate in our multivariable analysis can be explained by the death of patients in which the program was discontinued. Contrary to other reports showing an increased mortality rate for patients treated with intensive chemotherapy [6, 14, 16], we did not detect significant differences between treatment schedules. However, these data should be interpreted with caution, considering that these patients may have been older or less fit when the disease developed.

Our study found an overall mortality rate of 46.4%, a value comparable to other publications [9–10]. We found that COVID-19 was the primary or a main reason for death in most cases (70%), although we deliberately decided to focus our study on overall mortality rather than on attributable mortality. Even though attributable mortality might seem more appropriate for evaluating the impact of an infection in HM patients, it can also be more easily influenced by the subjective judgment of the local physician, and consequently less reliable when used in a risk factor assessment. Conversely, the overall mortality rate is not influenced by subjective interpretations and, therefore, it is more reliable for our study aim, even when the potential role of other confounding factors, e.g., primarily leukemia progression, is taken into account. We observed an increased mortality rate associated with age and active malignancy, in agreement with previously published data [4, 9]. In addition, comorbidities and sex did not impact on mortality rate, contrary to other reports [9, 17], but still consistent with the previously published study from the EPICOVIDEHA registry [4].

Finally, we performed a time-dependent analysis, showing that the overall survival rate of patients diagnosed with COVID-19 from January to August 2020 was significantly lower compared to that of patients diagnosed more recently, confirming an improvement of the clinical outcome of AML patients throughout the different pandemic waves. These observations could be explained by a combination of factors, including improved management of the disease and detection of a larger number of asymptomatic/mild cases by screening programs. Although the current data on the SARS-CoV-2 pandemic show a progressive decrease of hospitalization and deaths in the overall population, HM patients remain a particularly high-risk population.

Our study has some limitations. First, those intrinsically linked to the initial project design. We did not request any details regarding COVID-19 therapeutic approaches, as these were extremely heterogeneous and treatment recommendations changed quickly. Data on viral strains were only infrequently determined. In addition, only very few cases from our cohort (n=7) were documented as breakthrough infections in fully vaccinated patients, which did not allow us to conclude on vaccine effectiveness. Interestingly, this aspect was partially addressed by our previous preliminary data on HM vaccinated patients, which showed a mild decrease in mortality of vaccinated AML patients [29].

In conclusion, our study shows that COVID-19 in AML patients poses a serious challenge, as it adds a layer of complication which can lead to modified therapeutic algorithms. The mortality rate in this patient group was very high, even when the significant reduction over the pandemic course was considered. According to our results, the best approach to improve the survival of AML patients with COVID-19 seems to delay AML treatment, whenever possible.

Ethics and data protection

EPICOVIDEHA has been approved by the local Institutional Review Board and Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). The corresponding local ethics committee of each participating institution may approve additionally the EPICOVIDEHA study when applicable. EPICOVIDEHA is registered at <http://www.clinicaltrials.gov>, identifier NCT 04733729.

Declarations

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Author contributions

LP served as the principal investigator. FM, JSG and LP contributed to study design, study supervision, and data interpretation and wrote the paper. AB, PC, MH, NK, PK, AP, FP, AOC and LP conceived the study idea. LP, JSG, and FM did the statistical plan, analysis and interpreted the data. All the authors recruited participants and collected and interpreted data. All authors contributed to manuscript writing and review of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

JSG has received speaker honoraria from Gilead Nordica, outside the submitted work.

AG has been consultant and advisory board member for Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, and has received research grants from Saniona and Sanofi, outside the submitted work.

IE has provided lectures or advisory board consultation to MSD, GILEAD, Janssen, Fundación Publica Andaluza Progreso y Salud, Grupo Español de trasplante hematopoyético y Terapia celular (GETH) and Fundación Madrileña de Hematología y Hemoterapia, outside the submitted work.

JP has received research funding from MSD, personal fees from Gilead and Pfizer and is stockholder of AbbVie Inc. and NovoNordisk, outside the submitted work.

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Figures

Figure 1

Numbers of Reason(s) for death might be superadditive

AML, acute myeloid leukemia; **COVID-19**, coronavirus disease 2019; **EPICOVIDEHA**, COVID-19 study of the European Hematology Association

Figure 1

Flow-chart of registered AML patients. (*) in 5 patients it's not known when did they received the treatment; (**) number can be super-additive.

Figure 2

Overall survival status by timing of last received treatment.

* In one patient with induction as last chemotherapy strategy, information on treatment continuation after COVID-19 is missing. ** In one patient with no treatment delay, last chemotherapy strategy is unknown. Patients with allogeneic or autologous hematopoietic stem cell transplantation were included in "Reinduction" in this figure.

AML, acute myeloid leukemia; **COVID-19**, coronavirus diseases 2019

Figure 3

Treatment modification in AML patients with last treatment on-going < 1 month before COVID-19. (*) in one patient the last treatment strategy was unknown.

Figure 4

Figure 4

Overall survival status by modification of initial chemotherapeutic program due to COVID-19 diagnosis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FigureS1.Overall survival status by modification of initial chemotherapeutic program due to COVID19 diagnosis Onset.pdf](#)
- [FigureS2.Overall survival status by observation time Jan2020 to Aug2020 vs Sept2020 to Feb2021 vs Mar2021 to Sept2021.pdf](#)