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 dying 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 diagnosed with COVID-19 between February 2020 and October 2021. The vast majority were receiving or had received AML treatment in the preceding 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%), whereas in 3.9% of cases the reason was unknown. 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 better survival when AML treatment could be delayed (80%; $P<0.001$). Overall survival in patients with a diagnosis of COVID-19 between January 2020 and August 2020 was significantly lower than that in patients diagnosed between September 2020 and February 2021 and between March 2021 and September 2021 (39.8% *vs.* 60% *vs.* 61.9%, respectively; $P=0.006$). 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, whenever possible.

Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy often requiring immediate chemotherapy because of a 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] Although viral infections are less relevant than 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] Specific data on large cohorts of patients with long-term follow-up are, therefore, 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, par-

ticularly in patients with a simultaneous diagnosis of AML and COVID-19.

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.

Methods

Study design, patients, and procedures

This was an observational multicenter study of AML patients who developed COVID-19 between February 2020 and October 2021, with data from EPICOVIDEHA (registered with *www.clinicaltrials.gov*; ID NCT04733729), an international open web-based registry for hematologic malignancies and COVID-19 patients initiated in February 2020 by members of the Infections in Hematology Scientific Working Group 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). All consecutive AML patients diagnosed with COVID-19 were captured and registered in this web-based registry. The respective local ethics committee of each participating institution provided approval as appropriate. The methodology of EPICOVIDEHA has been described elsewhere.[18] The electronic case report form is accessible online at *www.clinicalsurveys.net* (EFS Summer 2021, TIVIAN GmbH, Cologne, Germany).[19] Each patient was reviewed and validated by infectious diseases and hematology experts. Inclusion criteria were: (i) active AML within the 5 years preceding the diagnosis of COVID-19; (ii) age ≥18 years old; and (iii) a laboratory-based diagnosis of COVID-19. Patients' conditions before COVID-19 (i.e., age, sex, AML status at COVID-19 diagnosis, comorbidities), AML clinical management, COVID-19 diagnosis and management, and outcome were also recorded. Information regarding AML treatment modifications (i.e., delay or discontinuation) due to COVID-19, and the contribution of the diagnosis of COVID-19 to AML relapse or status at the last day of follow-up was also collected. Status of the hematologic malignancy at the onset of COVID-19 and last follow-up was defined as active (onset, stable disease, refractory/resistant) or controlled (complete response) based on 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 groups according to period of diagnosis: (i) January to August 2020 (first global wave of the pandemic); (ii) September 2020 to February 2021 (diagnosed in the 2020-2021 New Year holiday period); and (iii) March to September 2021 (diagnosed after SARS-CoV-2 vaccines became available). Patients with incomplete data about COVID-19 diagnosis, AML treatment phase/disease status and date of last follow-up were excluded from the final analysis.

Study objectives

The primary objective of this study was to evaluate the epidemiology and outcome of AML patients with COVID-19. Secondary objectives were to estimate the prevalence of disease severity, to describe the overall case-fatality rate, and 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

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. A log-rank test was used to compare the survival probability of the patients included in the different models. A P-value ≤0.05 was considered statistically significant. SPSS v27.0 was employed for statistical analyses (SPSS, IBM Corp., Chicago, IL, USA).

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 centers and 20 countries around the world. Out of these patients, 168 (30.2%) were excluded from this analysis because of missing data. In 25 cases (6.4%), a diagnosis of acute promyelocytic leukemia (APL) was reported.

The demographic and clinical characteristics of the remaining 388 patients are shown in Table 1. Their median age was 59 years (IQR, 45-70) and there was a slight male predominance (52.6%). Most patients had at least one underlying comorbidity, with chronic heart disease (e.g., hypertension, obstructive arteriopathy, atrial fibrillation) being the most frequent, whereas 175 patients (45.1%) had comorbidities. At the time of the COVID-19 diagnosis, 196 patients (50.5%) had controlled AML, and 192 (49.5 %) had active disease, including 79 (20.4%) patients at the onset of their leukemia. Only 110 patients (28.3%) were not on

active treatment; of these 110 patients, only four were on best supportive care, 18 were at the disease onset, whereas the remaining cases were in complete remission or in off-treatment follow-up. Overall, 237 patients (64.6%) had received intensive chemotherapy and transplantation, which were 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 discontinued permanently, whereas in the remaining 68 (39.1%) it was delayed and resumed at a median of 1 month (IQR, 1-2) after the diagnosis of COVID-19, once a negative SARS-CoV-2 swab had been documented. At COVID-19 onset, 71 (18.3%) and 53 (13.7%) patients had neutrophil and lymphocyte counts below $0.5x10^9$/L and $0.2x10^9$/L, respectively. Two hundred and twenty patients (56.7%) had pulmonary symptoms at the onset of COVID-19, mainly cough and dyspnea, 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 criti-

Table 1. Demographic and clinical features of 388 patients with acute myeloid leukemia at the time of COVID-19 diagnosis.

	N	%
Sex		
Female	184	47.4
Male	204	52.6
Age, years		
Median (IQR)	59 (45-70)	
Range	18-89	
Comorbidities	213	54.9
AML status at COVID-19 diagnosis		
Controlled disease	196	50.5
Complete remission	196	50.5
Active disease	192	49.5
Onset	79	20.4
Refractory/resistant	113	29.2
Last/ongoing treatment strategy before COVID-19		
Treatment	367	94.6
Conventional chemotherapy	250	64.4
Last month	172	44.3
Last 3 months	46	11.9
>3 months	32	8.2
HSCT	72	18.6
Last month	8	2.1
Last 3 months	11	2.8
>3 months	53	13.7
Best supportive care	45	11.6
Last month	27	7.0
Last 3 months	9	2.3
>3 months	4	1.0
Not stated	5	1.3
No treatment	21	5.4
COVID-19 infection		
Critical infection	82	21.1
Severe infection	160	41.2
Mild infection	69	17.9
Asymptomatic	77	19.8
COVID-19 diagnosis		
Swab	376	96.9
BAL+swab	5	1.3
Serology	4	1.0
BAL	3	0.8

	N	%
Symptoms at COVID-19 onset		
Pulmonary	144	37.1
Screening	86	22.2
Extrapulmonary	82	21.1
Pulmonary + extrapulmonary	76	19.6
Neutrophils, x 10^9/L		
≤0.5	71	18.3
0.501-0.999	38	9.8
≥1	203	52.3
Lymphocytes, x 10^9/L		
≤0.2	53	13.7
0.201-0.499	56	14.4
≥0.5	211	54.4
Stay during COVID-19		
Admitted to hospital	293	75.5
Duration of stay in hospital, days		
Median (IQR)	17 (8-30)	
Range	1-210	
Admitted to ICU	82	21.1
Duration of ICU stay, days		
Median (IQR)	10 (5-20)	
Range	1-111	
Invasive MV	63	16.2
Non-invasive MV	19	4.9
At home	117	30.2
Outcome		
Alive	208	53.6
Observation time, days		
Median (IQR)	325 (117-386)	
Range	3-639	
Dead	180	46.4
Observation time, days		
Median (IQR)	20 (8-58)	
Range	0-528	
Reason for death		
COVID-19	78	43.3
COVID-19 + HM	48	26.7
HM	47	26.1
Unknown reasons	7	3.9

COVID-19: coronavirus disease 2019; IQR: interquartile range; AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; BAL: bronchoalveolar lavage; IQR: interquartile range; ICU: intensive care unit; MV: mechanical ventilation; HM: hematologic malignancy.

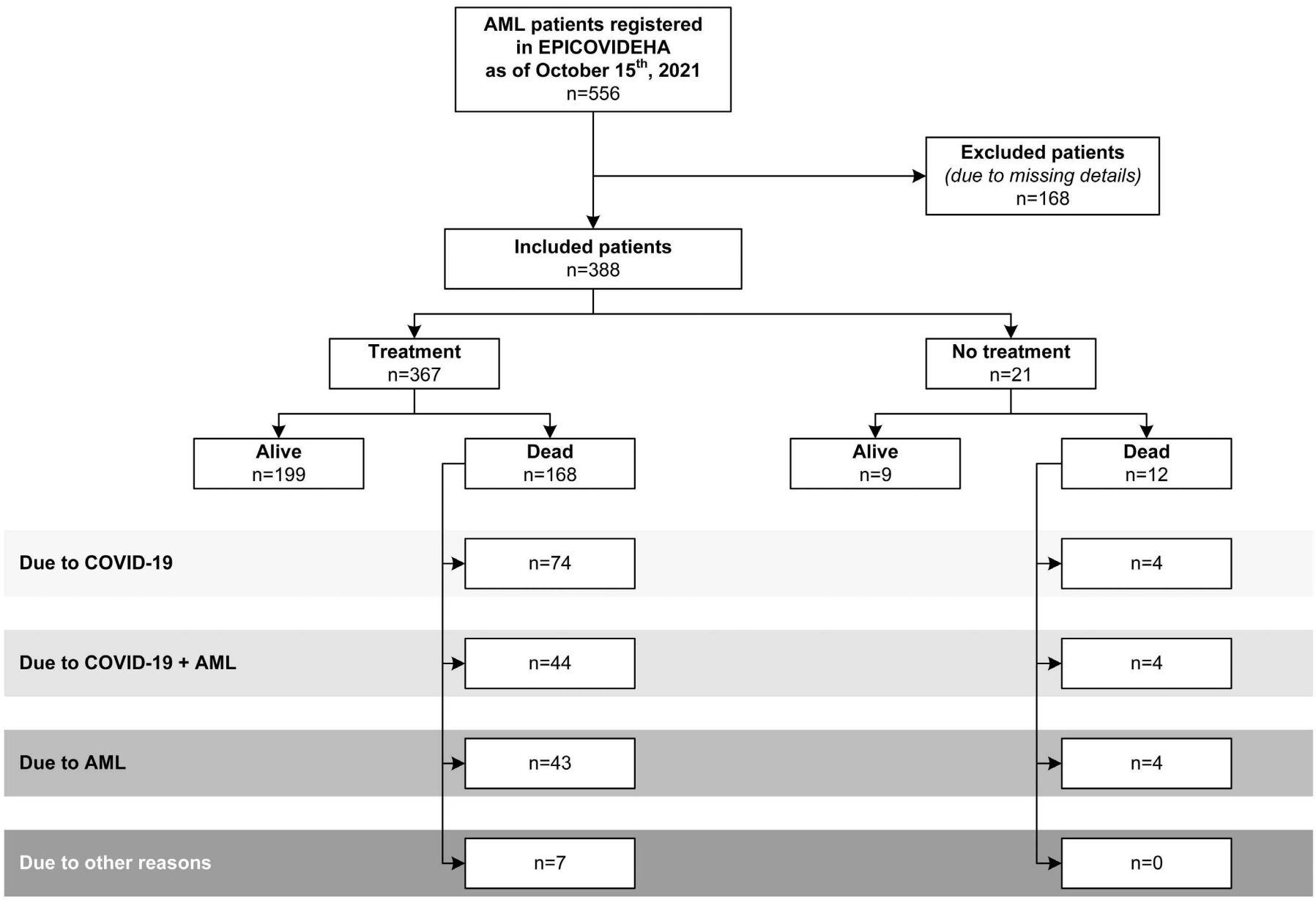

Figure 1. Flow-chart of registered patients with acute myeloid leukemia. For five patients, it is not known when they received their treatment. Numbers for the reasons of death may be super-additive. AML: acute myeloid leukemia; COVID-19: coronavirus disease 2019; EPICOVIDEHA; COVID-19 study of the European Hematology Association.

cal in 82 patients (21.1%), severe in 160 (41.2%), mild in 69 (17.9%), and asymptomatic in the remaining cases (19.8%). Overall, 293 patients (75.5%) were hospitalized during their SARS-CoV-2 infection for a median of 17 days (IQR, 8-30). Eighty-two patients (21.1%) were admitted to an intensive care unit for a median stay of 10 days (IQR, 5-20), 63 (76.8%) of whom required invasive mechanical ventilation. After a median follow-up of 325 days (IQR, 3-639), 180 patients (46.4%) had 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 seven patients (3.9%) (Table 1, Figure 1). The mortality rate of patients with ongoing or recent (<1 month before COVID-19 diagnosis) AML treatment, like those treated 1 to 3 months prior to their COVID-19 diagnosis, was significantly higher than that of patients receiving treatment until 3 months or earlier before the diagnosis COVID-19 (P<0.001) (Figure 2). When considering AML patients whose last chemotherapy was administered within the month before the COVID-19 diagnosis, a higher mortality rate was observed in 68 (80.9%) patients who discontinued treatment, regardless of the treatment phase (Figure 3). Of note, patients who discontinued treatment were not different in terms of median age, but more often had at least one comorbidity and had a slightly but not statistically significant worse clinical presentation of COVID-19. A significantly lower overall mortality rate was observed in patients in whom chemotherapy was delayed (overall mortality rate: 18.4%, 9/49), as opposed to that of patients whose treatment was not delayed (37.5%, 9/24) (P<0.001), with the only exception of the re-induction subgroup of patients (Figures 3 and 4). The overall mortality rate of patients in induction (67.1%, n=51) or re-induction (77.7%, n=28) was higher than that of patients receiving consolidation (20%, n=10) during the last month prior to COVID-19 (P<0.001). Interestingly, we did not find any statistically significant difference in terms of survival between patients in complete remission (off-treatment) and those in complete remission but under consolidation treatment (mortality rate: 20.2% *vs.* 24.1%; P=0.677). In the univariable analysis, several factors were associated with an increased mortality (Table 2): older age, previous comorbidities (i.e., chronic heart disease or renal impairment), active malignancy, critical COVID-19, or permanent AML treatment discontinuation. Contrariwise, hav-

ing a neutrophil or lymphocyte count above 0.5x10^9/L and 0.2x10^9/L, respectively, AML treatment >3 months before COVID-19 diagnosis and AML treatment delay were associated with a reduced mortality. In the multivariable model, active disease (hazard ratio [HR]=4.197, 95% confidence interval [95% CI]: 2.196-8.020; *P*<0.001), older age (HR=1.016, 95% CI: 1.004-1.028; *P*=0.012), and treatment discontinuation (HR=4.417, 95% CI: 2.306-8.460; *P*<0.001) were associated with a higher mortality, as opposed to treatment delay, which was found to be protective (HR=0.367, 95% CI: 0.151-0.891; *P*=0.027). After a time-dependent analysis, it was observed that overall survival in patients diagnosed

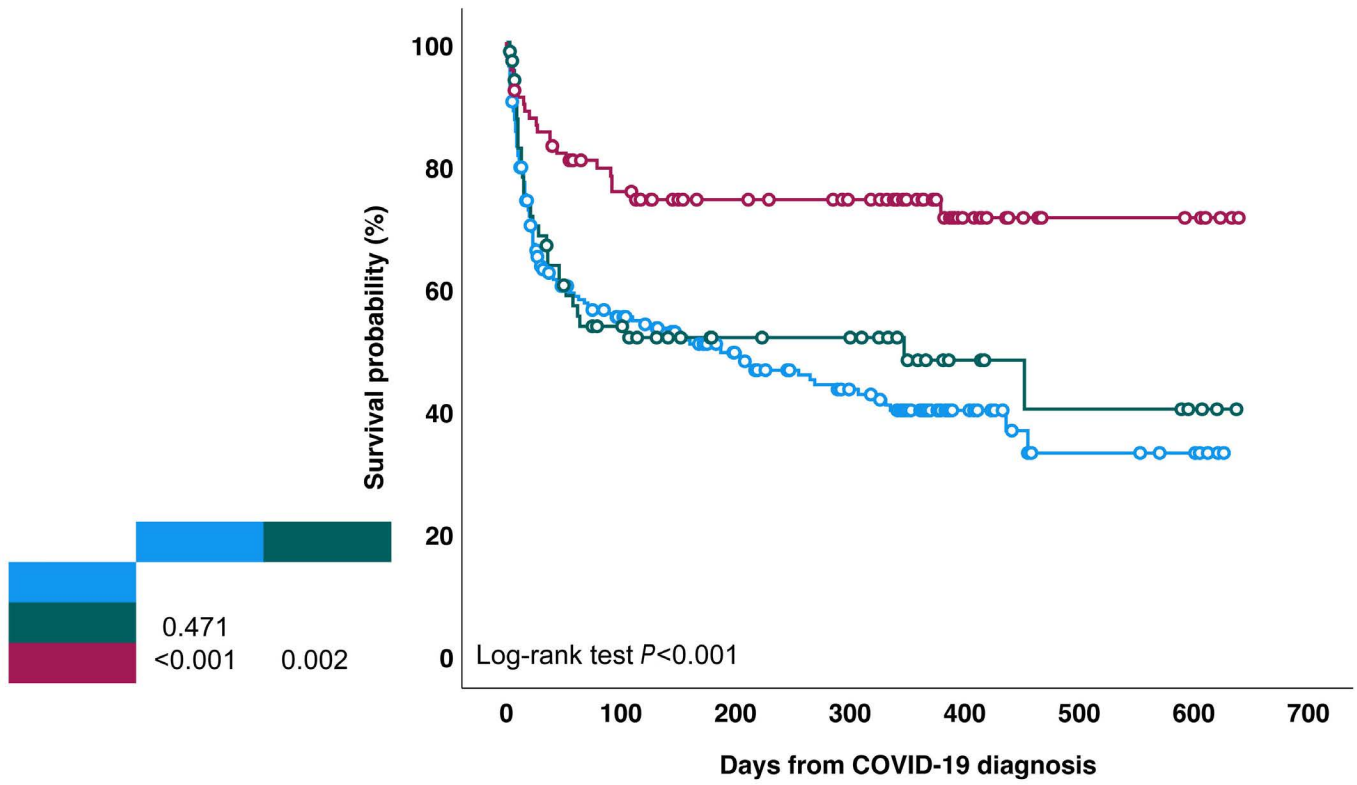

Figure 2. Survival probability by timing of last received treatment. AML: acute myeloid leukemia; COVID-19: coronavirus disease 2019; tx: treatment.

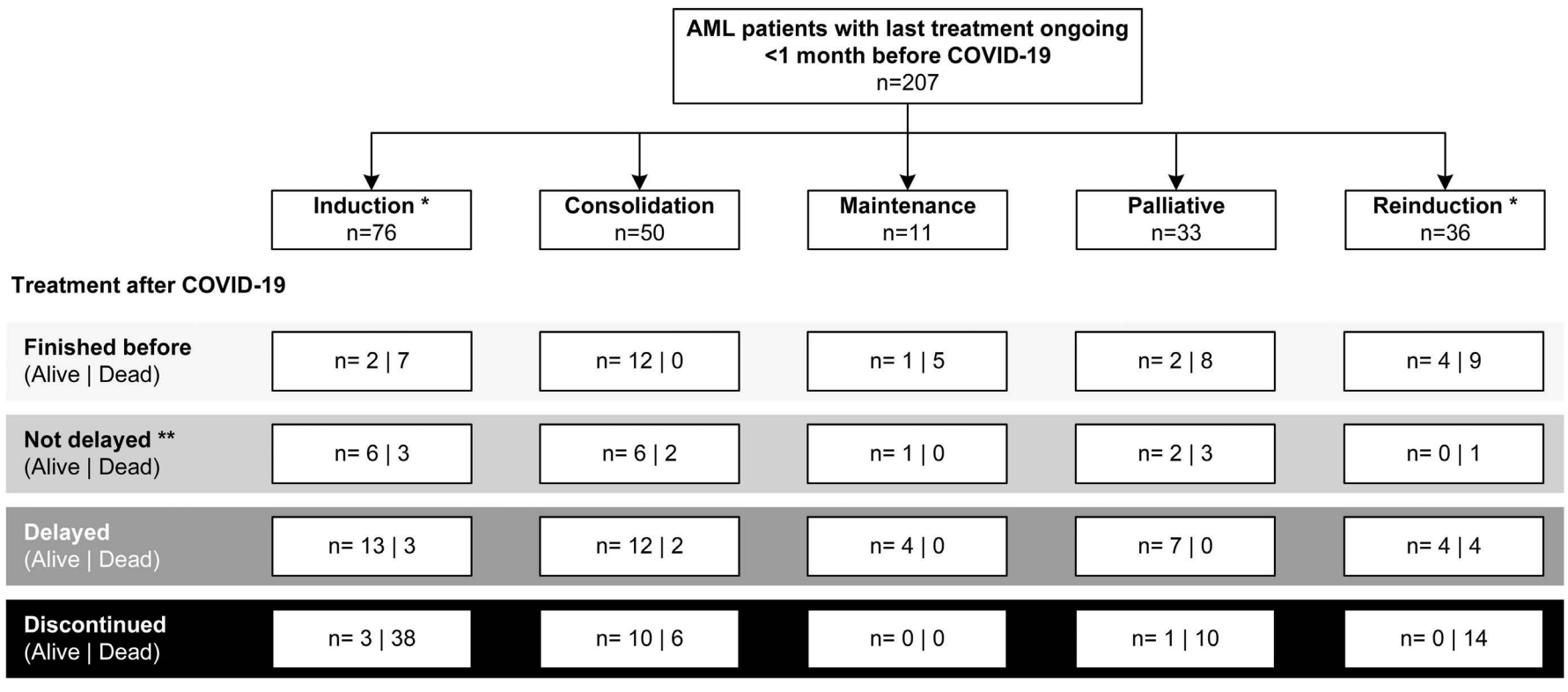

Figure 3. Treatment modification in patients with acute myeloid leukemia whose last treatment was ongoing less than 1 month before COVID-19. In one patient the last treatment strategy was unknown. *In one patient with induction as last chemotherapy strategy, information on treatment continuation after COVID-19 is missing. **In one patient with no treatment delay, the last chemotherapy strategy is unknown. Patients who underwent allogeneic or autologous hematopoietic stem cell transplantation were included in “Reinduction” in this figure. AML: acute myeloid leukemia; COVID-19: coronavirus disease 2019.

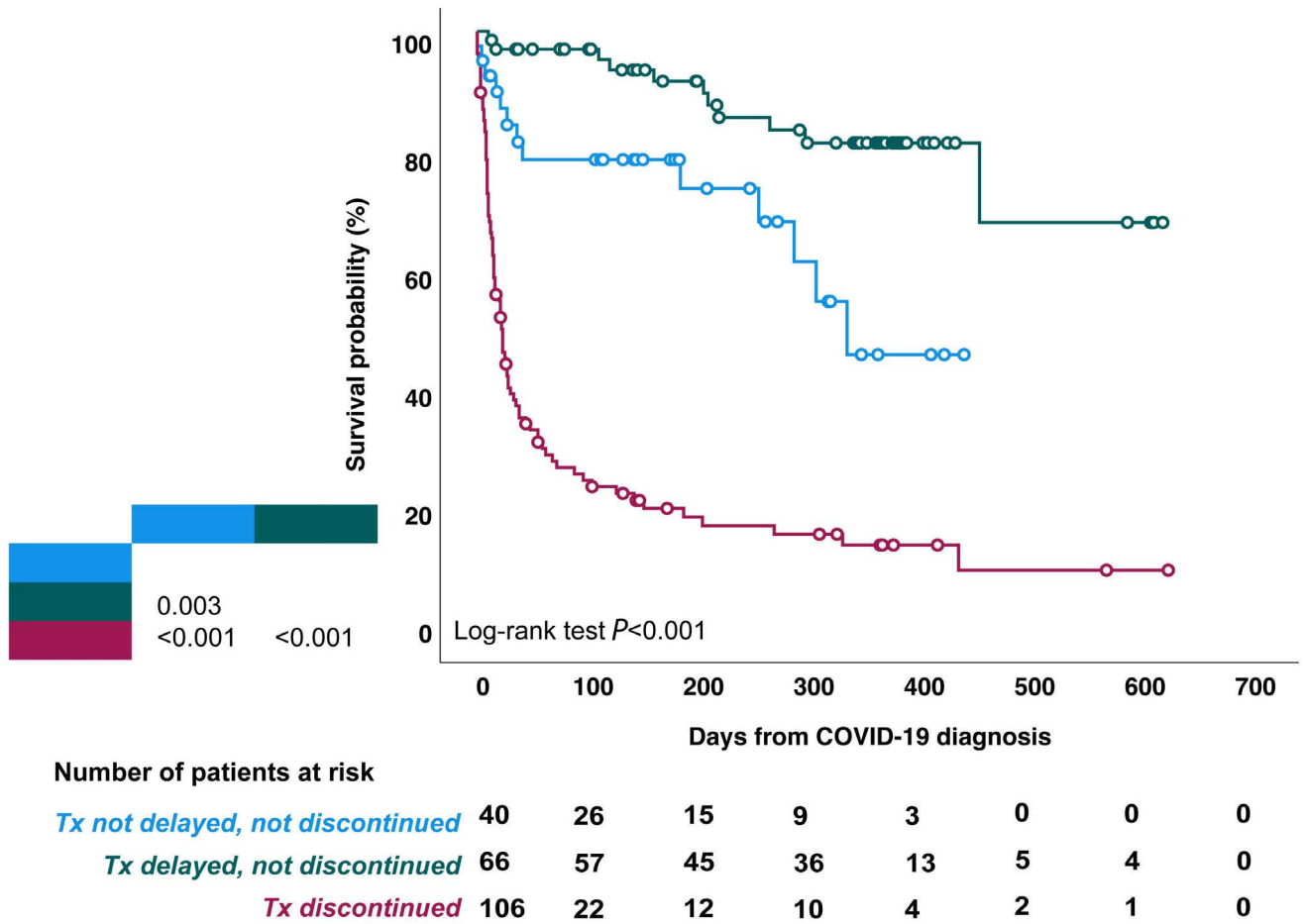

Figure 4. Survival probability by modification of initial chemotherapeutic program due to COVID-19 diagnosis. COVID-19: coronavirus disease 2019; Tx: therapeutic program for acute myeloid leukemia.

with COVID-19 between January 2020 and August 2020 was significantly lower than that of patients who were diagnosed between September 2020 and February 2021 and between March 2021 and September 2021 (39.8% *vs.* 60% *vs.* 61.9%, respectively; *P*=0.006) (*Online Supplementary Figure S2*).

Table 3 presents the demographic and clinical features of the 79 patients with a simultaneous diagnosis of AML and COVID-19. In 18 patients (22.8%), COVID-19 was diagnosed before the start of induction, resulting in a treatment delay. Overall survival was higher among patients whose treatment was delayed (80%) than among those whose treatment was not delayed and not discontinued (64%) or was discontinued (6%) (*P*<0.001) (Table 3, *Online Supplementary Figure S1*). Finally, a separate sub-analysis was carried out focusing on AML patients receiving consolidation treatment (*Online Supplementary Figure S3*), relapsed/refractory patients being given re-induction (*Online Supplementary Figure S4*) and patients in complete remission (*Online Supplementary Figure S5*), confirming the better clinical outcome in patients in whom treatment was delayed.

Discussion

There is a gap of knowledge regarding COVID-19 in AML patients, as the current evidence is restricted to small cohorts of patients, case reports/series, or expert opinions.[9-17] This gap has made it difficult to establish the best strategy to manage AML patients during the pandemic.[22,23] Taken together, the current evidence suggests that AML patients often present with a severe clinical form of COVID-19, frequently with respiratory distress and a very high mortality rate, between 40 and 50% higher than that in the pre-vaccine era. Here we present, to the best of our knowledge, the largest survey of AML patients with COVID-19, with 388 patients reported from 132 institutions, with a special focus on their long-term follow-up. The data presented in our manuscript confirm that AML patients frequently have a severe clinical presentation of COVID-19, mainly with respiratory symptoms, and a high rate of intensive care unit admission, even among those with low-risk AML (i.e., acute promyelocytic leukemia).

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 impairment of neutrophil function 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 7 days immediately prior to and up to 28 days after SARS-CoV-2 diagnosis was associated

Table 2. Overall mortality predictors of death in patients with acute myeloid leukemia and COVID-19.

Overall mortality	Univariable				Multivariable			
			95% CI				95% CI	
	P value	HR	Lower limit	Upper limit	*P* value	HR	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
AML 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 10^9/L								
≤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 10^9/L								
≤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
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	-	-	-	-

95% CI: 95% confidence interval; HR: hazard ratio;; COVID-19, coronavirus disease 2019; AML: acute myeloid leukemia; Tx: therapeutic program for AML.

with an increased odds of death.[27] In our study, severe neutropenia was found to be significantly associated with the risk of death in univariable analysis, but the 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 have been based only on expert opinions and consensus,[22,23] given the lack of evidence-based algorithms to guide clinicians. This is particularly relevant for treatment-naïve AML patients with a concomitant symptomatic SARS-CoV-2 infection. The general recommenda-

Table 3. Demographic and clinical features of 79 patients with acute myeloid leukemia at the onset of their malignancy at COVID-19 diagnosis.

	Overall (N=79)		No treatment before COVID-19 (N=18)		Induction treatment before start of COVID-19 (N=61)	
	N	%	N	%	N	%
Sex						
Female	35	44.3	10	55.6	25	41.0
Male	44	55.7	8	44.4	36	59.0
Age, years						
Median (IQR)	65 (50-76)		66 (55-72)		65 (50-76)	
Range	18-88		18-88		19-86	
Comorbidities	48	60.8	11	61.1	37	60.7
COVID-19 infection						
Critical infection	23	29.1	3	16.7	20	32.8
Severe infection	36	45.6	8	44.4	28	45.9
Mild infection	10	12.7	4	22.2	6	9.8
Asymptomatic	10	12.7	3	16.7	7	11.5
COVID-19 diagnosis						
Swab	76	96.2	18	100	58	95.1
BAL+swab	2	2.5	0	0	2	3.3
Serology	1	1.3	0	0	1	1.6
Symptoms at COVID-19 onset						
Pulmonary	39	49.4	9	50.0	30	49.2
Extrapulmonary	14	17.7	4	22.2	10	16.4
Pulmonary + extrapulmonary	13	16.5	2	11.1	11	18.0
Screening	13	16.5	3	16.7	10	16.4
Neutrophils, x10^9/L°						
≤0.5	24	30.4	4	22.2	20	32.8
0.501-0.999	10	12.7	2	11.1	8	13.1
≥1	34	43.0	9	50.0	25	41.0
Lymphocytes, x10^9/L°						
≤0.2	11	13.9	1	5.6	10	16.4
0.201-0.499	11	13.9	2	11.1	9	14.8
≥0.5	50	63.3	13	72.2	37	60.7
Stay during COVID-19						
Admitted to hospital	73	92.4	15	83.3	58	95.1
Duration of stay in hospital, days						
Median (IQR)	20 (9-32)		14 (4-24)		22 (9-36)	
Range	2-106		2-86		3-106	
Admitted to ICU	23	29.1	3	16.7	20	32.8
Duration of ICU stay, days						
Median (IQR)	7 (4-12)		5 (2-10)		7 (4-12)	
Range	1-32		2-10		1-32	
Invasive mechanical ventilation	18	22.8	1	5.6	17	27.9
Non-invasive mechanical ventilation	4	5.1	0	0.0	4	6.6
At home	10	12.7	4	22.2	6	9.8
Outcome						
Alive	26	32.9	8	44.4	18	29.5
Observation time, days						
Median (IQR)	266.5 (85-386)		266.5 (122-353)		277.5 (75-408)	
Range	11-613		44-613		11-601	

Continued on following page.

Dead	53	67.1	10	55.6	43	70.5
Observation time, days						
Median (IQR)	19 (6.5-57)		14 (5-48)		21 (7-63)	
Range	0-528		0-528		0-331	
Reason for death°						
COVID-19	20	37.7	3	30.0	17	39.5
COVID-19 + hematologic malignancy	16	30.2	4	40.0	12	27.9
Hematologic malignancy	17	32.1	3	30.0	14	32.6

°Data can be super additive. COVID-19: coronavirus disease 2019; IQR: interquartile range; BAL: bronchoalveolar lavage; ICU: intensive care unit.

tion 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 initiation is often recommended in routine practice, especially in patients with *de novo* or 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. A Spanish group made a similar finding:[9] in their cohort of 108 patients, a lower mortality rate was observed in patients in whom chemotherapy was delayed as compared to the rate in those with or without treatment modification. However, their results were observed only in the univariable analysis. Our multivariable model confirmed that a delay in a chemotherapeutic program 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 whom a delay in AML induction 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 whom 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 patients given different treatment schedules, including those based on demethylating agents. However, these data should be interpreted with caution, considering that these patients may have been older or less fit when their disease developed.

The overall mortality rate in our study was 46.4%, a value comparable to that in 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 patients with a hematologic malignancy, 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 it is, therefore, 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 have an impact on mortality rate, unlike in other studies,[9,17] but 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 than that of patients diagnosed more recently, confirming an improvement in the clinical outcome of AML patients throughout the different waves of the pandemic. 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, patients with a hematologic malignancy 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 the therapeutic approaches to COVID-19, as these were extremely heterogeneous and treatment recommendations changed quickly. Data on viral strains were only infrequently available and about one third of patients were excluded from the final analysis because of missing information. In addition, only a very few cases from our cohort (n=7) were documented as breakthrough infections in fully vaccinated patients, which did not allow us to draw conclusion on vaccine effectiveness. Interestingly, this aspect was partially addressed by our previous preliminary data on vaccinated patients with a hematologic malignancy, which showed a mild decrease in mortality of vaccinated AML patients.[29] Finally, it is not possible to exclude a potential selection

bias in patients, since AML patients who were able to delay treatment could have had less aggressive disease, whereas those who permanently discontinued the treatment might have had serious COVID-19 complications, becoming unfit for further therapy.

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 group of patients was very high, even taking into consideration the significant reduction over the course of the pandemic. According to our findings, the best approach to improve the survival of AML patients with COVID-19 seems to be to delay treatment for the hematologic malignancy, whenever possible.

Disclosures

No conflicts of interest to disclose.

Contributions

LP was the principal investigator. FM, JSG and LP contributed to the study design, study supervision, and data interpretation and wrote the paper. AB, PC, MH, NK, PK, AP, FP, AOC and LP conceived the idea of the study. LP, JSG and FM did the statistical plan and analysis and interpreted the data. All the authors recruited participants and collected and interpreted data. All authors contributed to writing and reviewing 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.

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Data-sharing statement

Data will be available from the corresponding author upon reasonable request.

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References

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
2. Ferrara F, Schiffer C. Acute myeloid leukaemia in adults. Lancet. 2013;381(9865):484-495.
3. Fontana L, Strasfeld L. Respiratory virus infections of the stem cell transplant recipient and the hematologic malignancy patient. Infect Dis Clin North Am. 2019;33(2):523-544.
4. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 infection in adult patients with hematologic malignancies: a European Hematology Association survey (EPICOVIDEHA). J Hematol Oncol. 2021;14(1):168.
5. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with hematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7(10):e737-e745.
6. García-Suárez J, de la Cruz J, Cedillo Á, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. J Hematol Oncol. 2020;13(1):133.
7. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25):2881-2892.
8. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol. 2020;21(10):1309-1316.
9. Palanques-Pastor T, Megías-Vericat JE, Martínez P, et al. Characteristics, clinical outcomes, and risk factors of SARS-COV-2 infection in adult acute myeloid leukemia patients: experience of the PETHEMA group. Leuk Lymphoma. 2021;62(12):2928-2938.
10. Fagundes EM, Neto NN, Caldas LM, et al. Mortality by COVID-19 in adults with acute myeloid leukemia: a survey with hematologists in Brazil. Ann Hematol 2021;101(4):923-925.
11. Ghandili S, Pfefferle S, Roedl K, et al. Challenges in treatment of patients with acute leukemia and COVID-19: a series of 12 patients. Blood Adv. 2020;4(23):5936-5941.
12. Taurino D, Frigeni M, Grassi A, et al. Concurrent diagnosis of acute myeloid leukemia and symptomatic COVID-19 infection: a case report successfully treated with azacitidine-venetoclax combination. Mediterr J Hematol Infect Dis. 2021;13(1):e2021057.
13. Ferrara F, Zappasodi P, Roncoroni E, Borlenghi E, Rossi G.

Impact of COVID-19 on the treatment of acute myeloid leukemia. Leukemia. 2020;34(8):2254-2256.
14. Núñez-Torrón C, García-Gutiérrez V, Tenorio-Núñez MC, Moreno-Jiménez G, López-Jiménez FJ, Herrera-Puente P. Poor outcome in patients with acute leukemia on intensive chemotherapy and COVID-19. Bone Marrow Transplant. 2021;56(1):267-269.
15. Singh S, Singh J, Paul D, Jain K. Treatment of acute leukemia during COVID-19: focused review of evidence. Clin Lymphoma Myeloma Leuk. 2021;21(5):289-294.
16. Demichelis-Gómez R, Alvarado-Ibarra M, Vasquez-Chávez J, et al. Treating acute leukemia during the COVID-19 pandemic in an environment with limited resources: a multicenter experience in four Latin American countries. JCO Glob Oncol. 2021;7:577-584.
17. Buyuktas D, Acar K, Sucak G, et al. COVID-19 infection in patients with acute leukemia: Istanbul experience. Al J Blood Res. 2021;11(4):427-437.
18. Salmanton-García J, Busca A, Cornely OA, et al. EPICOVIDEHA: a ready to use platform for epidemiological studies in hematological patients with COVID-19. Hemasphere. 2021;5(7):e612.
19. Tivian XI GmbH. Experience-management software. https://www.tivian.com/de/. Accessed December 28, 2021.
20. COVID-19 clinical management. Living guidance World Health Organization. January 15, 2021. WHO/2019-nCoV/clinical/2021.1.
21. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242.
22. Zeidan AM, Boddu PC, Patnaik MM, et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts. Lancet Haematol. 2020;7(8):e601-e612.
23. Raza A, Assal A, Ali AM, Jurcic JG. Rewriting the rules for care of MDS and AML patients in the time of COVID-19. Leuk Res Rep. 2020;13:100201.
24. Yarza R, Bover M, Paredes D, et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: analysis of clinical features and predictive factors for severe respiratory failure and death. Eur J Cancer. 2020;135:242-250.
25. Ljungman P, de la Camara R, Mikulska M, et al. COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. Leukemia. 2021;35(10):2885-2894.
26. Piñana JL, Martino R, García-García I, et al. Risk factors and outcome of COVID-19 in patients with hematological malignancies. Exp Hematol Oncol. 2020;9:21.
27. Stahl M, Narendra V, Jee J, et al. Neutropenia in adult acute myeloid leukemia patients represents a powerful risk factor for COVID-19 related mortality. Leuk Lymphoma. 2021;62(8):1940-1948.
28. Röllig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020;136(7):823-830.
29. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 in vaccinated adult patients with hematological malignancies. Preliminary results from EPICOVIDEHA. Blood. 2022;139(10):1588-1592.