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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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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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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.

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Data sharing statement

Data will be available by reasonable request directed to the corresponding author.

Clinical trial registration

EPICOVIDEHA is registered at http://www.clinicaltrials.gov, identifier NCT 04733729.

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Running head

COVID-19 in adult AML patients

Disclosure of conflict of interest

All the authors have no disclosures to declare for this submitted paper.

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%), 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 an improved survival when AML treatment could be delayed (80%; p<0.001). Overall survival in patients with COVID-19 diagnosis between January 2020 and August 2020 was significantly lower than those 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). 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 hematological malignancy (HM) 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.

Methods

Study design, patients, and procedures

This is an observational multicenter study of AML patients who developed COVID-19 between February 2020 and October 2021, with data from EPICOVIDEHA (www.clinicaltrials.gov; ID NCT04733729), an international open web-based registry for HM and COVID-19 patients 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). 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 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 patient was reviewed and validated by infectious diseases and hematology experts. Inclusion criteria were: a) active AML within the last five years before COVID-19 diagnosis, b) patients ≥18 years old, and c) laboratory-based diagnosis of COVID-19. Patients' conditions pre-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 in AML relapse or status at last day of follow up was also collected. Status of HM at COVID-19 onset 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 time periods as follows: a) January to August 2020 (first global wave of the pandemic); b) September 2020 to February 2021, (patients diagnosed in the New Year holiday time of 2020-2021); and c) March to September 2021, (patients diagnosed after the 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: 1) to estimate the prevalence of disease severity; 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

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).

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 due to 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. 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; out of these 110 patients, only 4 were on best supportive care, 18 were at the disease onset, whereas the remaining cases were in complete remission and follow-up off-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, once that a negative SARS-CoV-2 swab was documented. At COVID-19 onset, 71 (18.3%) and 53 (13.7%) patients had neutrophil and lymphocyte counts below 0.5 x 10^9/L and 0.2 x 10^9/L, respectively. Two hundred and twenty patients (56.7%) had pulmonary symptoms at COVID-19 onset, 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 critical 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 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.

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 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). Of note, patients who discontinued treatment had no difference in terms of median age, had more often at least one co-morbidity and presented a slightly but not statistically significant worse clinical presentation of COVID-19. Furthermore, a significantly lower overall mortality rate was observed in patients with chemotherapy delay (overall mortality rate: 18.4%, 9/49), as opposed to those patients with no delay (37.5%, 9/24) (p<0.001), with the only exception of re-induction sub-group of patients (Figure 3 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). Interestingly, we did not find any statistically significant difference in terms of survival between patients in CR (off-treatment) and those in CR 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 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 x 10^9/L and 0.2 x 10^9/L, 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, 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 with COVID-19 diagnosis between January 2020 and August 2020 was significantly lower than those 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; Figure S2).

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 (treatment delayed: 80% *vs* treatment not delayed and not discontinued: 64% *vs* treatment discontinued: 6%; p<0.001; Table 3, Figure S1). Finally, a separate sub-analysis has been carried out focusing on AML patients receiving consolidation treatment (Figure S3), relapsed/refractory patients getting reinduction (Figure S4) and patients in CR (Figure S5), confirming the better clinical outcome observed in patients with treatment delay.

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 of COVID-19, mainly with respiratory symptoms, and a high rate of ICU admission, even in patients with low-risk AML (i.e. APL).

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, 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 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 and about one third of patients were excluded from the final analysis due to missing information. 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] Finally, it's not possible to exclude a potential patient selection bias, since AML patients who were able to delay treatment could have less aggressive disease, whereas those who permanently discontinued the treatment might have had serious COVID-19 complication 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 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.

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Tables

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
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 three months	46	11.9
> 3 months	32	8.2
HSCT	72	18.6
Last month	8	2.1
Last three months	11	2.8
> 3 months	53	13.7
Best supportive care	45	11.6
Last month	27	7.0
Last three 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
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 in hospital	293	75.5
Duration of the stay in hospital, median days (IQR) [range]	17 (8-30) [1-210]	
ICU stay	82	21.1
Duration of the ICU stay, median days (IQR) [range]	10 (5-20) [1-111]	
Invasive mechanical ventilation	63	16.2
Non-invasive mechanical ventilation	19	4.9
At home	117	30.2
Outcome		
Alive	208	53.6
Observation time, median days (IQR) [range]	325 (117-386) [3-639]	

	n	%
Dead	180	46.4
Observation time, median days (IQR) [range]	20 (8-58) [0-528]	
Reason for death°		
COVID-19	78	43.3
COVID-19 + Hematological malignancy	48	26.7
Hematological malignancy	47	26.1
Unknown reasons	7	3.9

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

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

OVERALL MORTALITY	Univariable				Multivariable			
	p value	HR	95% CI Lower limit	95% CI Upper limit	p value	HR	95% CI Lower limit	95% CI 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 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	-	-	-	-

AML, acute myeloid leukemia; **COVID-19**, coronavirus disease 2019; **ICU,** intensive care unit; **HSCT,** hematopoietic stem cell transplantation; **mm^3**, cubic meters; **TX,** therapeutic program for AML.

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

	Overall *(n=79)*		No treatment before COVID-19 *(n=18)*		Induction treatment start before COVID-19 *(n=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 10^9/L)°						
≤ 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 10^9/L)°						
≤ 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
≥ 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-		277.5 (75-408) [11-601]	

	Overall *(n=79)*		**No treatment before COVID-19** *(n=18)*		**Induction treatment start before COVID-19** *(n=61)*	
	n	**%**	**n**	**%**	**n**	**%**
				613]		
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

Figure legends

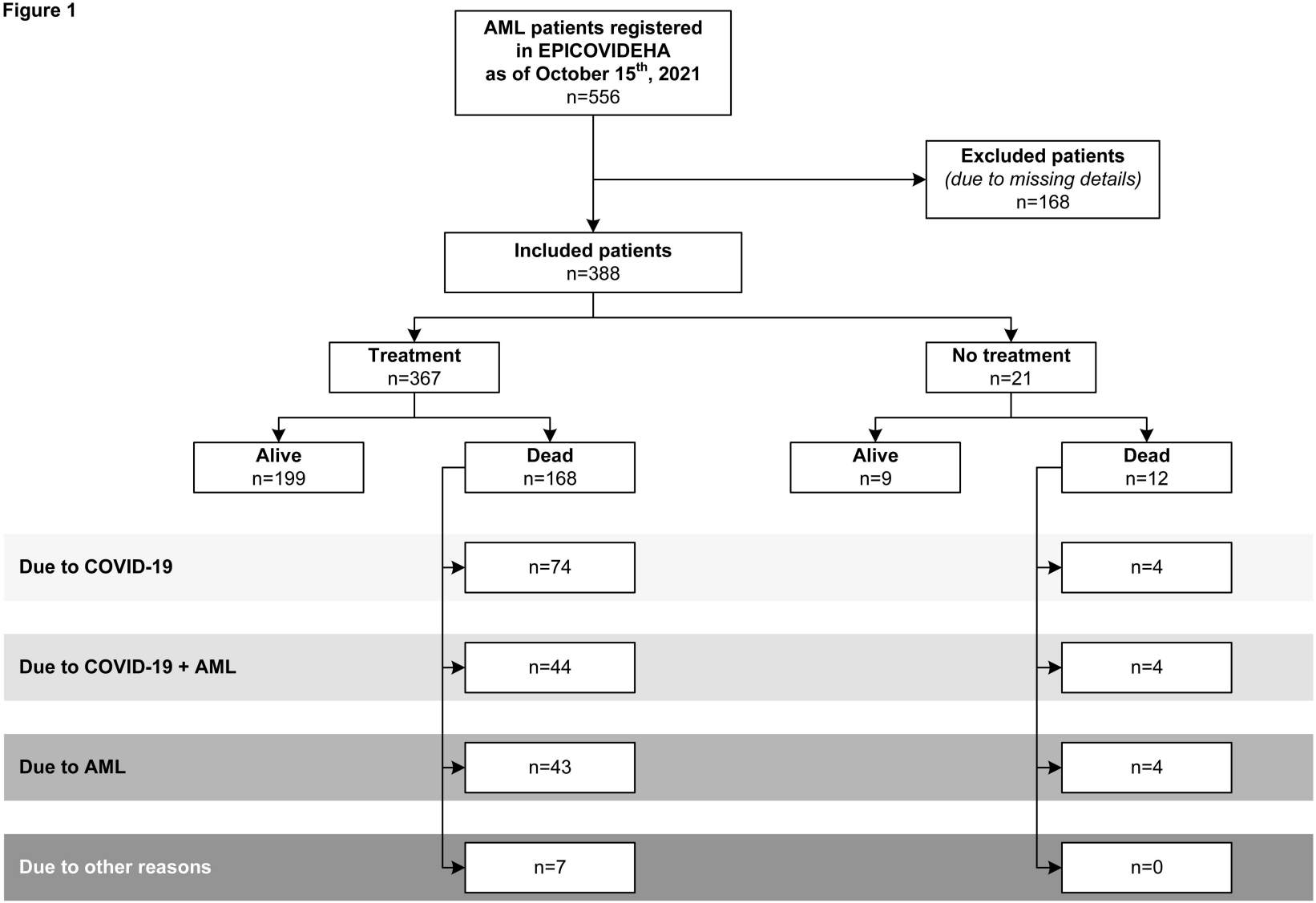
Figure 1. Flow-chart of registered AML patients. (*) in 5 patients it's not known when did they received the treatment; (**) number can be super-additive.

Figure 2. Survival probability by timing of last received treatment.

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. Survival probability by modification of initial chemotherapeutic program due to COVID-19 diagnosis.

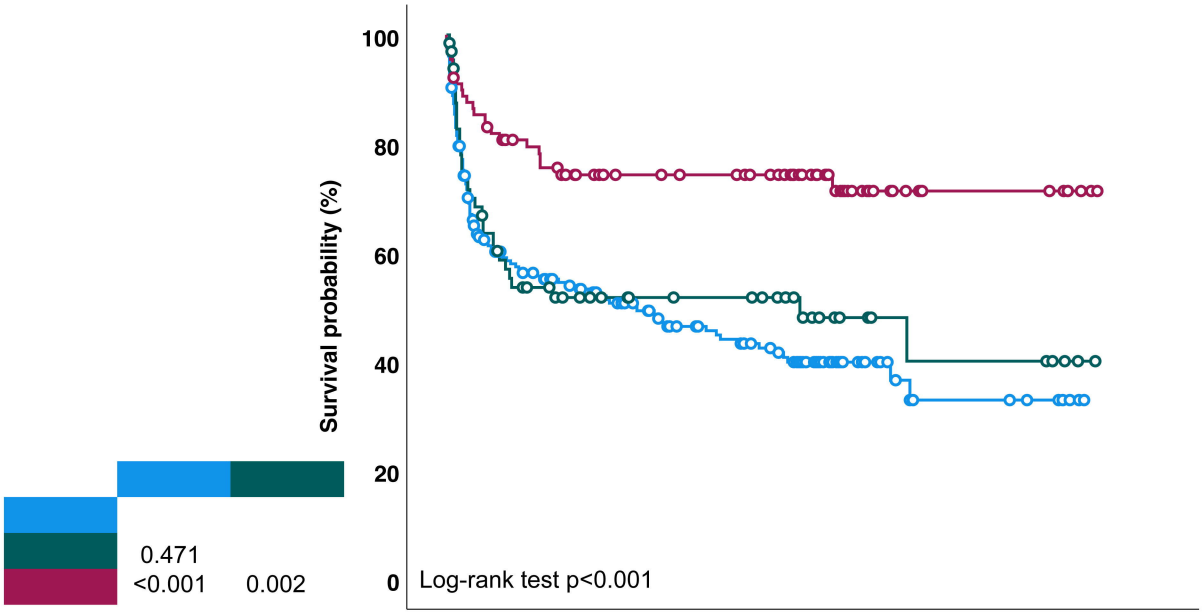
Figure 1



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

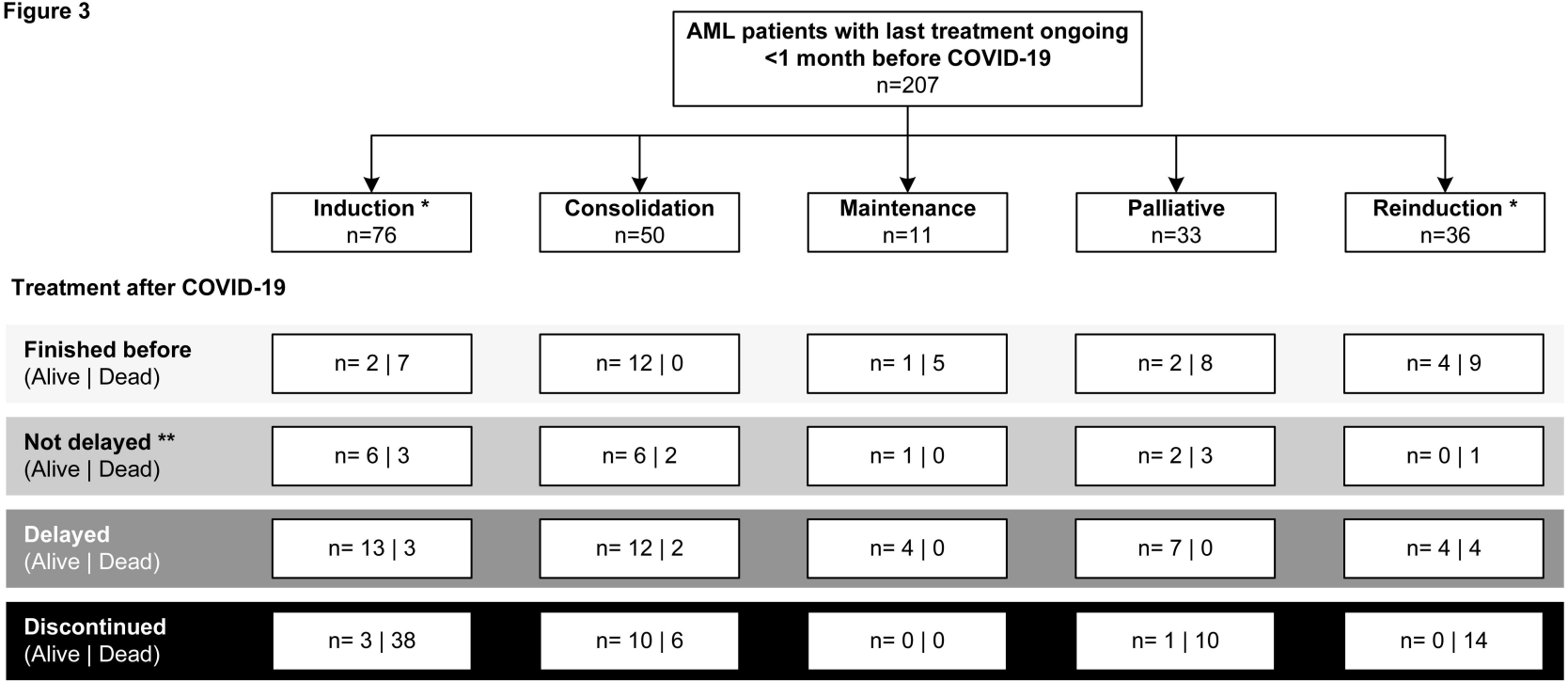
Figure 2



Number of patients at risk

AML tx in the last month before COVID-19	206	94	69	52	19	7	5	0
AML tx 1-3 months before COVID-19	66	30	21	20	8	5	3	0
>AML tx >3 months before COVID-19	89	59	48	42	18	6	5	0

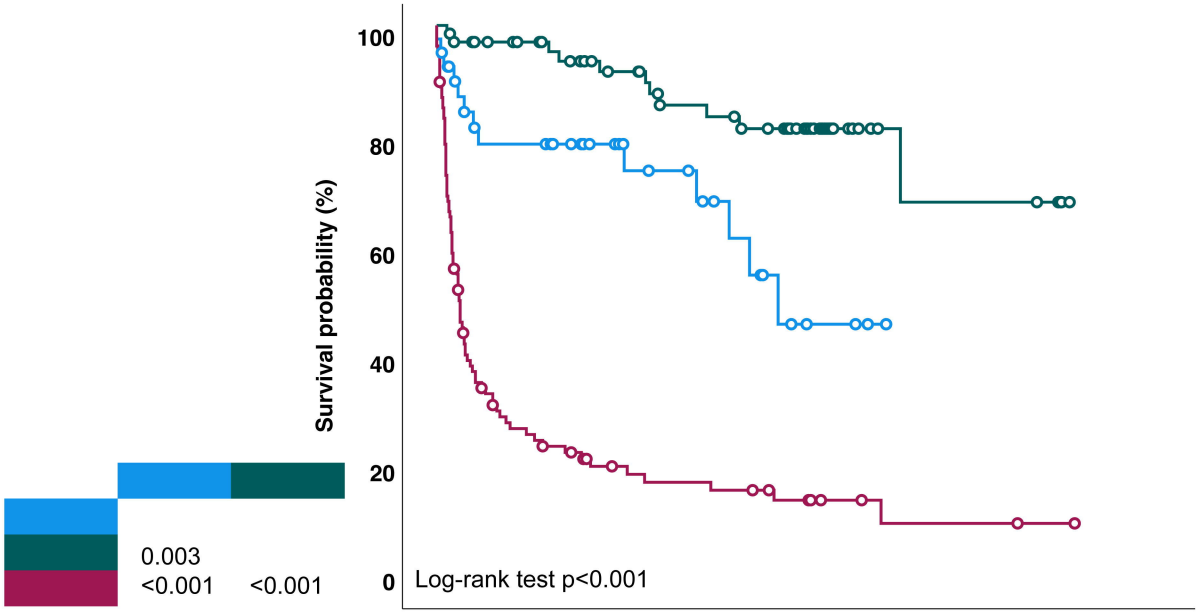
Figure 3



* 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

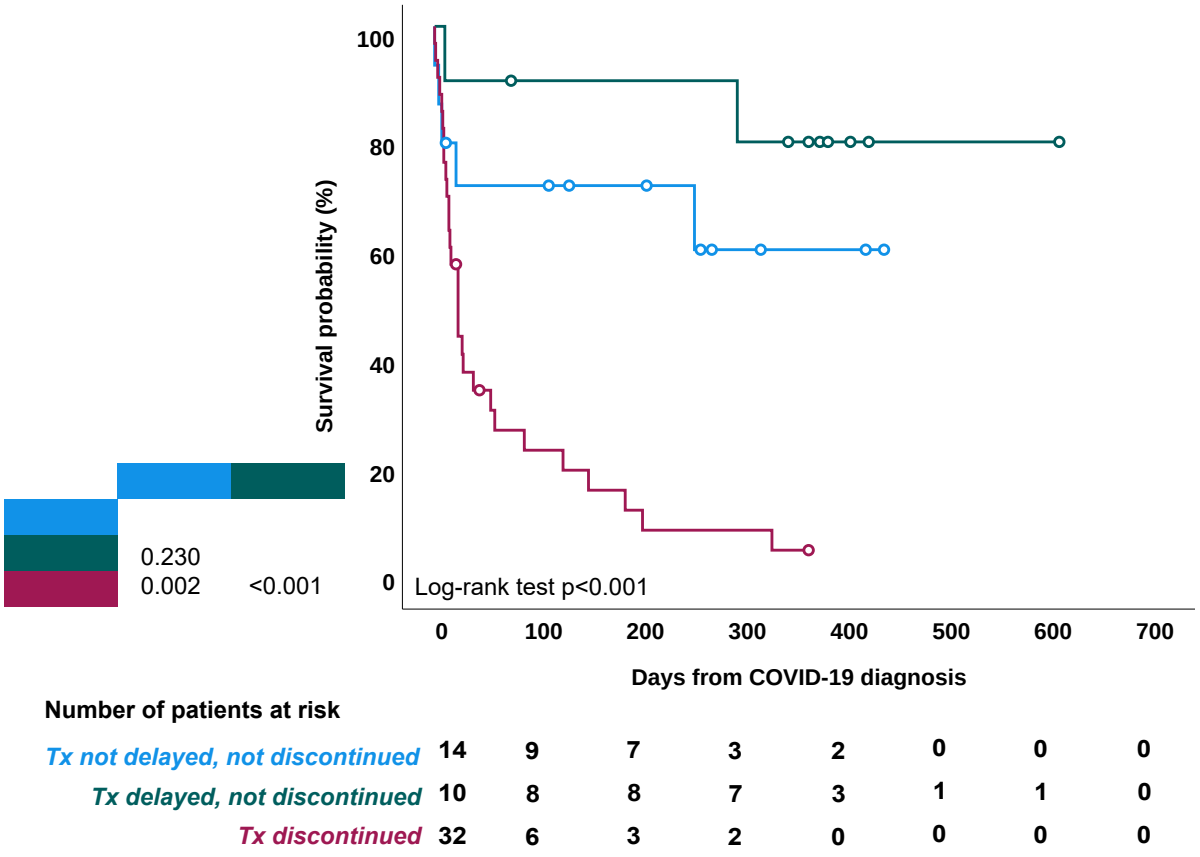
Figure 4



Number of patients at risk

Tx not delayed, not discontinued	40	26	15	9	3	0	0	0
Tx delayed, not discontinued	66	57	45	36	13	5	4	0
Tx discontinued	106	22	12	10	4	2	1	0

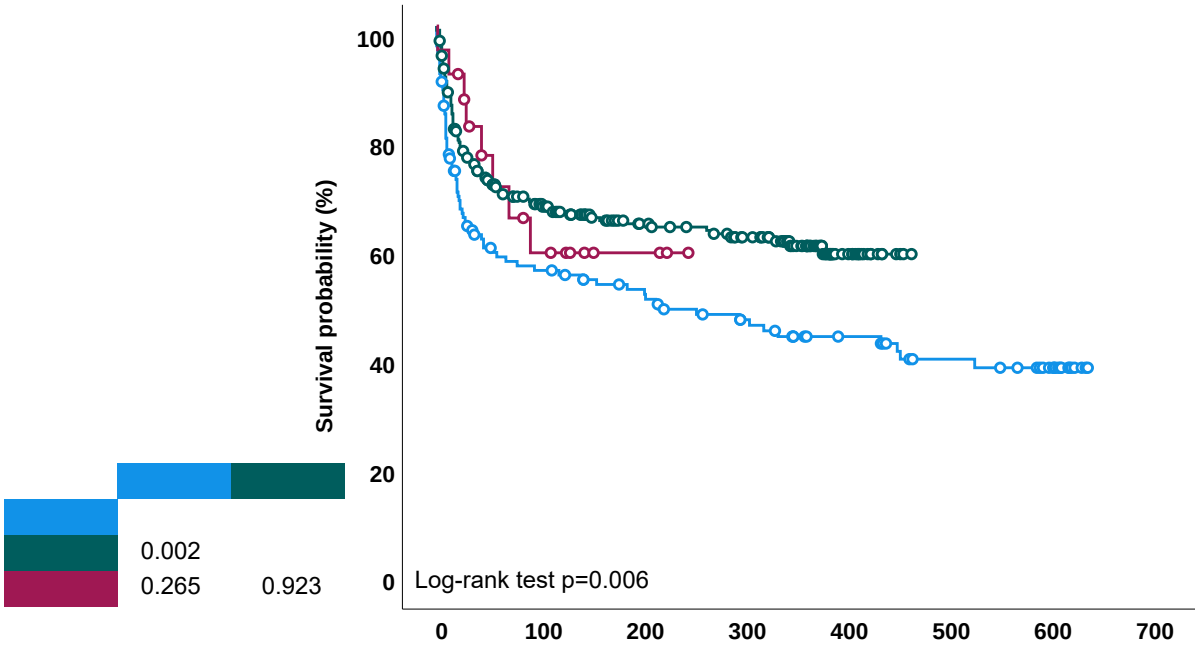
Figure S1



Number of patients at risk

Tx not delayed, not discontinued	14	9	7	3	2	0	0	0
Tx delayed, not discontinued	10	8	8	7	3	1	1	0
Tx discontinued	32	6	3	2	0	0	0	0

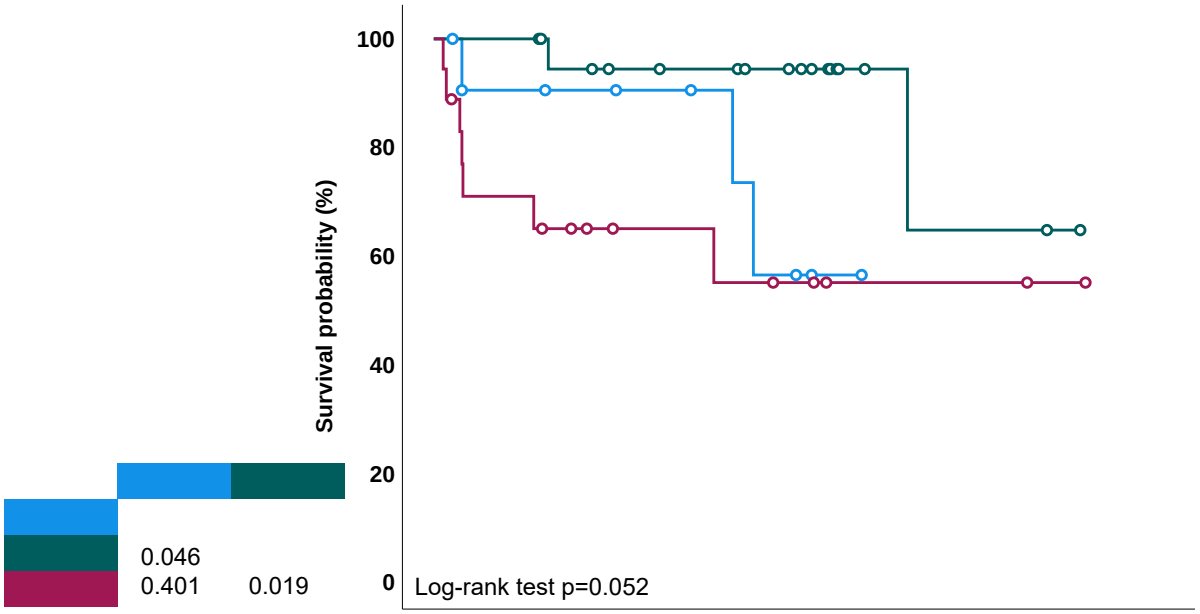
Figure S2



Number of patients at risk

January-August 2020	127	58	49	38	28	20	14	0
September 2020-February 2021	238	130	95	81	19	0	0	0
March-September 2021	21	8	3	0	0	0	0	0

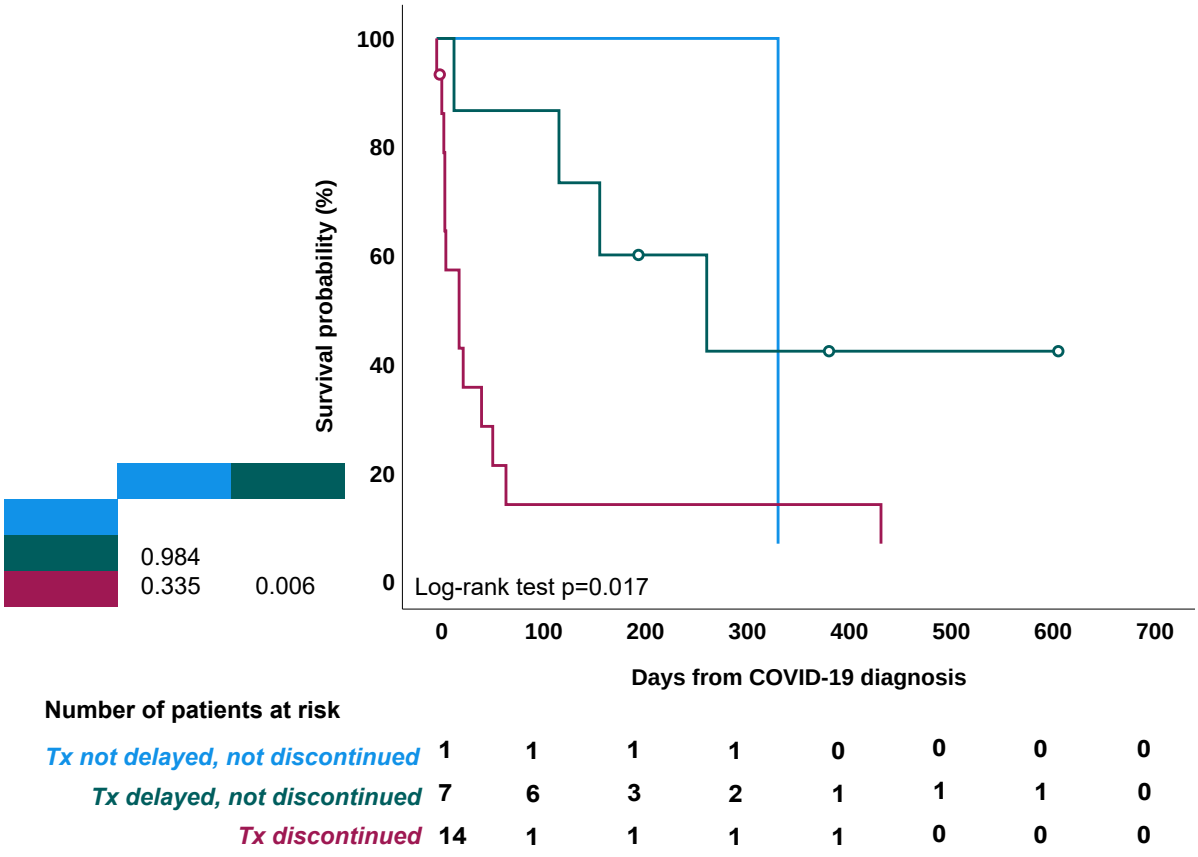
Figure S3



Number of patients at risk

Tx not delayed, not discontinued	11	8	6	4	1	0	0	0
Tx delayed, not discontinued	19	18	14	11	4	2	1	0
Tx discontinued	17	10	6	5	2	2	1	0

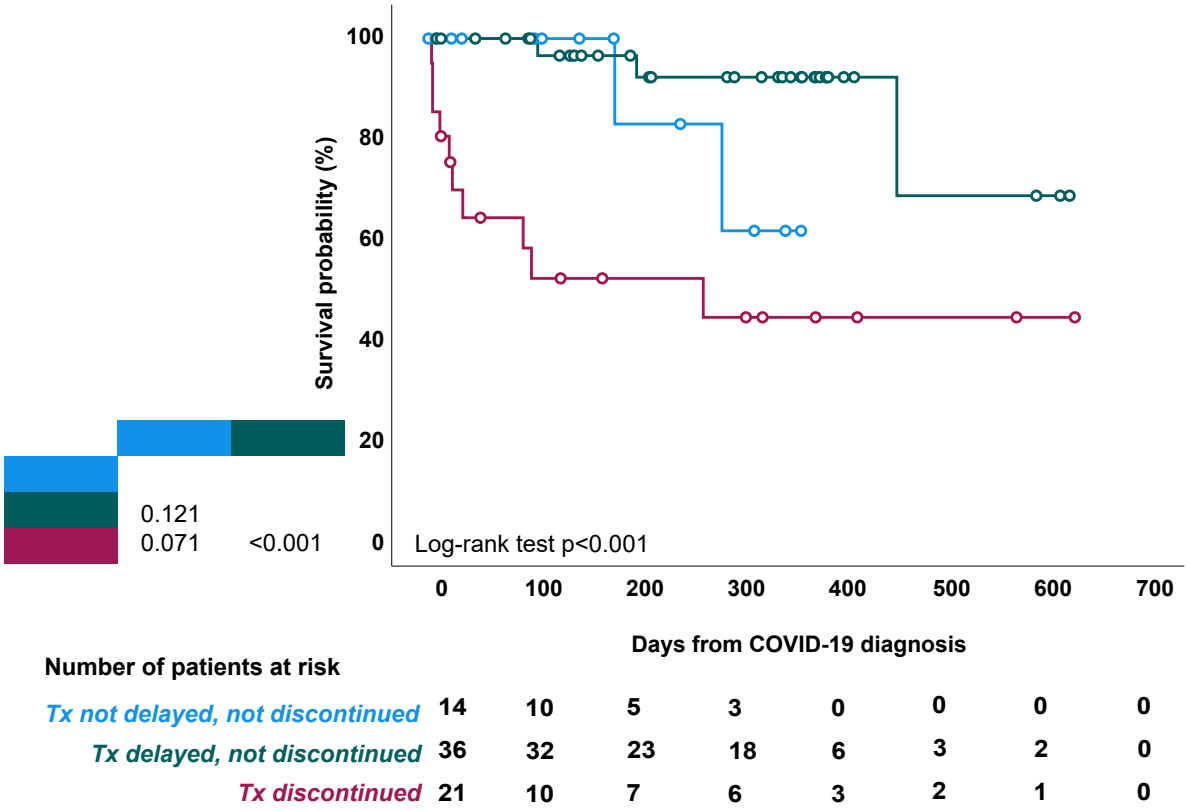
Figure S4



Number of patients at risk

Tx not delayed, not discontinued	1	1	1	1	0	0	0	0
Tx delayed, not discontinued	7	6	3	2	1	1	1	0
Tx discontinued	14	1	1	1	1	0	0	0

Figure S5



Number of patients at risk

Tx not delayed, not discontinued	14	10	5	3	0	0	0	0
Tx delayed, not discontinued	36	32	23	18	6	3	2	0
Tx discontinued	21	10	7	6	3	2	1	0

Supplementary figures' legend

Figure S1. Survival probability by modification of initial chemotherapeutic program due to COVID-19 in 79 with concomitant AML and COVID-19 diagnosis.

Figure S2. Survival probability by observation time (Jan-2020 to Aug-2020 *vs* Sept-2020 to Feb-2021 *vs* Mar-2021 to Sept-2021).

Figure S3. Survival probability by modification of initial chemotherapeutic program due to COVID-19 diagnosis in patients receiving consolidation treatment.

Figure S4. Survival probability by modification of initial chemotherapeutic program due to COVID-19 diagnosis in relapsed/refractory patients receiving reinduction treatment.

Figure S5. Survival probability by modification of initial chemotherapeutic program due to COVID-19 diagnosis in CR patients.