Sultan Qaboos University Med J, November 2024, Vol. 24, Iss. 4, pp. 568–574, Epub. 27 Nov 24
Submitted 9 Jul 24
Revision Req. 11 Aug 24; Revision Recd. 20 Aug 24
Accepted 27 Aug 24
https://doi.org/10.18295/squmj.11.2024.078

CLINICAL & BASIC RESEARCH

Impact of COVID-19 on the Clinical Characteristics and Outcomes of Patients with Acute Leukaemia

An academic centre experience

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abstract: ***Objectives:*** This study aimed to identify the impact of the COVID-19 pandemic on the frequency, clinical characteristics and outcomes of patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). ***Methods:*** This retrospective cohort study included all patients treated at Sultan Qaboos University Hospital in Muscat, Oman with AML or ALL from January 2017 to December 2021. Data were obtained from the electronic medical record, and patients diagnosed before the start of the COVID-19 pandemic were compared with those diagnosed during the pandemic using appropriate statistical tests. ***Results:*** A total of 151 patients with ALL (n = 58) and AML (n = 93) were included, of whom 78 were diagnosed before the COVID-19 pandemic and 73 during the pandemic. The rate of acute leukaemia increased during the pandemic ($P = 0.039$). The clinical characteristics and molecular profiles were similar between the 2 periods, except for platelet count which was higher during the pandemic compared to before the pandemic (median platelet count: 55×10^9/L versus 47×10^9/L; $P = 0.02$). No significant difference was found in the number of FLT3-positive AML; however, the number of NPM1-mutated AML cases was higher during the pandemic ($P = 0.02$). The number of Philadelphia-positive ALL cases remained consistent between the 2 time periods. The complete remission ($P = 0.48$) and the overall survival rates were similar ($P > 0.05$). ***Conclusion:*** Except for an increased rate of acute leukaemia and a lower platelet count, the COVID-19 pandemic did not impact the presentation and outcomes of acute leukaemia.

Keywords: Haematologic Neoplasms; COVID-19; Acute Myeloid Leukemia; Acute Lymphoblastic Leukemia; Survival; Oman.

Advances in Knowledge

- *The rate of acute leukaemia increased after the COVID-19 pandemic.*
- *Patients with acute leukaemia had lower platelet counts at presentation after the COVID-19 pandemic.*

Application to Patient Care

- *The outcomes of treatment of acute leukaemia remain unchanged after the COVID-19 pandemic.*
- *The same therapeutic approaches that were practiced before the COVID-19 pandemic should be practiced after.*

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After its emergence, the disease rapidly evolved into a global pandemic, exerting a significant impact on human health within a short period of time. In December 2019, a notable surge in cases presenting with symptoms such as dry cough, fever and fatigue was observed, primarily in Wuhan, China.[1,2] Subsequently, a proportion of patients developed severe pneumonia and acute respiratory distress syndrome.[3]

Numerous studies have demonstrated that patients with haematological malignancies are particularly vulnerable to COVID-19. The risks of morbidity and mortality are increased in these patients due to their compromised immune systems and the administration of immunosuppressive therapies.[4–6] These patients are at a higher risk of developing severe clinical complications, which can have a detrimental impact on their life expectancy.

Several studies have investigated the outcomes of patients with haematological malignancies who were diagnosed with COVID-19 infection compared to the general population and individuals with haematological malignancies who were not infected with COVID-19.[7–9] However, at present, there are no studies investigating the impact of COVID-19 on the incidence rates, clinical characteristics and outcomes in patients with acute leukaemia. Therefore, this study hypothesised that the changes in the immune system after COVID-19 infection increase the risk of developing malignancies and lead to more severe disease and worse outcomes. To test this hypothesis, this study compared the rates, clinical characteristics and outcomes of patients with acute leukaemia before and during the COVID-19 pandemic.

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Methods

This single centre retrospective cohort study included adolescent and adult patients, aged 13 and above, with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), who were treated at Sultan Qaboos University Hospital, Muscat, Oman, from January 2017 to December 2021. This study included patients newly diagnosed with AML or ALL based on the World Health Organization 2016 diagnostic criteria. Patients aged 13 to 18 years were treated under adult care and were included in the study population, and data were collected using electronic medical records (EMR). The pre-COVID-19 pandemic timeframe was considered to be from January 2017 to December 2019 and the pandemic period was considered to be from January 2020 to the end of the study period.

The following data were collected: age, gender, haemoglobin level, platelet count, white blood cell count, lactate dehydrogenase, weight and height. Molecular tests such as NPM1, FLT3, PML-RARA, BCR-ABL1, KMT2A and bone marrow blast percentage were recorded. The clinical features of the patients, including the presence of central nervous system disease, Eastern Cooperative Oncology Group performance status and any comorbidities, were also collected. Additionally, data on bone marrow transplants and COVID-19 infection were recorded. To investigate patient outcomes, data on complete remission and the date of the last follow-up were collected to determine overall survival. All variables were collected at the time of diagnosis.

All the collected data were recorded and analysed using R, Version 4.3.3.[10] Descriptive statistics were employed to describe the data. Frequencies, percentages, range, median and interquartile range (IQR) were reported for categorical variables. Continuous variables were summarised by presenting the median and IQR. Categorised variables were analysed by calculating the percentage and number of cases. T-test was used to compare continuous variables before and during the COVID-19 pandemic. Chi-squared tests were employed for categorised variables. The annual rates before and during the COVID-19 pandemic were directly estimated, and the rates were compared using a Poisson regression model. Survival analysis was performed using the Kaplan–Meier method, and comparisons were made using the Log-Rank test. A *P* value of 0.05 was considered statistically significant.

Approval for the study was obtained from the Medical Research Ethics Committee at the College of Medicine and Health Sciences (MREC#2354).

Results

The data from 493 patients with AML and ALL were retrieved using the diagnosis search from the EMR. Of these, 342 cases (69.4%) were excluded because they were below the age of 13, not newly diagnosed during the study period, presented incomplete information, were referred from other tertiary centres or experienced a relapse during the study period. Therefore, a total of 151 cases (30.6%) were finally included in this study [Figure 1]. There were 85 males and 66 females with a median age of 35 years (range: 20–52 years). Patients with AML accounted for 61.6% of the cases (n = 93), followed by ALL with 38.4% (n = 58). Within the whole cohort, 24.5% of patients (n = 37) developed COVID-19, and 34.4% (n = 52) underwent bone marrow transplant. The baseline characteristics of patients were similar before and during the COVID-19 pandemic except for platelet count, which was higher during the pandemic (*P* = 0.02) [Table 1]. When the group were divided into ALL and AML, the baseline characteristics were similar when comparing before and during the COVID-19 pandemic [Tables 2 and 3].

The total number of patients with acute leukaemia before the COVID-19 pandemic was 78, with an average of 26 per year. Comparatively, there were 73 patients during the COVID-19 pandemic, with an average of 36 per year. This difference was found to be statistically significant (*P* = 0.039), indicating a notable change in the rate of new acute leukaemia during the pandemic. The odds ratio (OR) was calculated as 1.4 with a confidence interval (CI) of 1.01–1.93.

Regarding AML before COVID-19, there were 47 patients in the preceding 3 years, with an average of 16 per year. Comparatively, the number of AML patients was 46 in 2 years during the pandemic, with

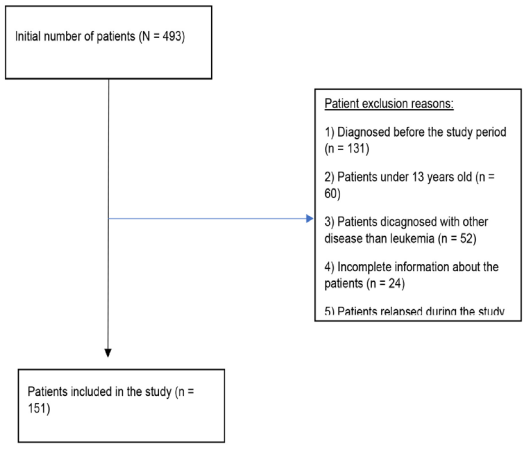

Figure 1: Flowchart showing patient selection for this study.

Table 1: Characteristics of patients with acute leukaemia (N = 151)

Characteristic	n (%)*			*P* value
	Total (n = 151)	Pre-COVID-19 (n = 78)	During COVID-19 (n = 73)	
Median age in years (IQR)	35 (20–52)	40 (23.2–57.5)	31 (18.7–46)	0.05
Male gender	85 (56.3)	43 (55.1)	40 (54.8)	0.99
Haematological malignancy				
AML	93 (61.6)	47 (60.3)	45 (61.6)	0.98
ALL	58 (38.4)	31 (39.7)	28 (38.4)	
Median haemoglobin in mg/dL (IQR)	8.1 (7.4–9.5)	8.2 (7.3–9.8)	8 (7.4–9.3)	0.74
Median white blood cells × 10^9/L (IQR)	8.6 (2.8–37.2)	8.6 (3–37.5)	7.1 (2.6–33.4)	0.4
Median platelets × 10^9/L (IQR)	52 (25–117)	47 (25–87)	55 (28.7–160.2)	0.02
Median LDH in U/L (IQR)	411 (243–752)	407 (235–746)	427.5 (262–788)	0.36
Median bone marrow blast percentage at diagnosis (IQR)	70 (31–90)	70 (38.8–90)	69.4 (26.6–89.9)	0.61
Central nervous system dis-ease	23 (15.2)	14 (17.9)	9 (12.3)	0.46
Bone marrow transplant	52 (34.4)	24 (30.8)	27 (37.0)	
Mutation				
NPM1	15 (30)	6 (24)	9 (36)	0.35
FLT3	21 (42)	10 (40)	11 (44)	0.9
PML-RARA	5 (10)	3 (12)	2 (8)	0.78
BCR-ABL1	9 (18)	6 (24)	3 (12)	0.34
ECOG performance status				
0	7 (4.6)	3 (3.8)	6 (8.2)	
1	82 (54.3)	47 (60.2)	34 (46.5)	
2	61 (40.4)	27 (34.6)	33 (45.2)	
3	1 (0.7)	1 (1.3)	0 (0.0)	

IQR = interquartile range; AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; LDH = lactate dehydrogenase; ECOG = electrocorticography.
**The COVID-19 test status refers to COVID-19 infection at any time during the study's follow-up period*

an average of 23 per year, which is higher than the pre-pandemic period. Still, the difference was not statistically significant (OR = 1.43, 95% CI: 0.95–2.16; *P* = 0.08). Among the total number of patients with ALL, there were 30 in 3 years before the pandemic, with an average of 10 per pear. During the pandemic, this number increased to 28 in 2 years, with an average of 14 per year; the difference was not statistically significant (OR: 1.35, 95% CI: 0.79–2.27; *P* = 0.25).

Before the pandemic, the complete remission rate was 58% compared to 65% during the pandemic, a difference that was not statistically significant (*P* = 0.48), suggesting that the pandemic did not have a substantial impact on the complete remission rate in patients with acute leukaemia. The difference was not statistically significant when comparing the pre-pandemic period with the pandemic period in patients with AML (57% versus 55%; *P* = 0.99) or ALL (60% versus 81%; *P* = 0.13).

The overall survival probabilities in this cohort of patients were comparable pre- and post-COVID-19 pandemic. The overall survival rate for all patients with acute leukaemia at 1 year was 64% before and 68% during the pandemic, and the difference was not statistically significant (*P* = 0.7) [Figure 2]. The difference was also not statistically significant when comparing the 1-year overall survival probability pre-pandemic and during the pandemic period in patients with AML (61% versus 60%; *P* = 0.7) or ALL (71% versus 83%; *P* = 0.1) [Figure 3].

Discussion

This study hypothesised that the COVID-19 doesn't just impact the morbidity and mortality of individuals affected by it but also on the immune response of the survivors of this disease.[11] This study is the first to investigate the non-direct impact of COVID-19 on the clinical characteristics at presentation, the rates of acute leukaemia and the outcomes of treatment.

The most notable observation was the increased rate of acute leukaemia in the period after the

Table 2: Characteristics before and during the COVID-19 pandemic of patients with acute lymphoblastic leukaemia (n = 58)

Characteristic	n (%)*		*P* value
	During COVID-19	Before COVID-19	
Gender			0.99
Male	17 (60.7)	18 (60.0)	
Female	11 (39.3)	12 (40.0)	
Median finding			
Age in years (IQR)	25 (16–31.5)	25 (16–37)	0.31
Weight in kg (IQR)	59.7 (51.3–71.7)	63 (52.2–71.6)	0.8
Height in cm (IQR)	167 (157.8–175.5)	163 (155.5–175.5)	0.79
Haemoglobin in mg/dL (IQR)	7.9 (7.3–8.9)	9.1 (7.8–10.3)	0.3
white blood cells × 10^9/L (IQR)	22.8 (2.8–58.7)	7.4 (3.5–39.1)	0.91
Platelets × 10^9/L (IQR)	38 (22.4–133)	66 (29.7–111.7)	0.35
Lactate dehydrogen-ase in U/L (IQR)	586 (335.5–1023.5)	553 (214.5–1030)	0.76
Bone marrow blast percentage (IQR)	83 (45–91.8)	78 (1.4–85.8)	0.29
FLT3			0.6
Positive	0 (0.0)	1 (20.0)	
Negative	4 (100)	4 (80.0)	
KMT2A			0.19
Positive	0 (0.0)	0 (0.0)	
Negative	20 (100)	15 (100)	
BCR_ABL1			0.62
Positive	3 (15.0)	5 (26.3)	
Negative	17 (85.0)	14 (73.7)	
ECOG perfor-mance status			0.81
0	3 (10.7)	0 (0.0)	
1	14 (50.0)	16 (53.3)	
2	11 (39.3)	13 (43.3)	
3	0 (0.0)	1 (3.3)	
Central nervous system disease			0.99
Present	6 (21.4)	5 (16.7)	
Absent	22 (78.6)	25 (83.3)	
COVID-19 detec-tion			
Detected	14 (50.0)	2 (6.7)	
Not detected	14 (50.0)	28 (93.3)	
Bone marrow transplant			
Transplanted	11 (39.3)	9 (30.0)	
Not transplanted	17 (60.7)	21 (70.0)	

IQR = interquartile range; ECOG = electrocorticography.

**The COVID-19 test status refers to COVID-19 infection at any time during the study's follow-up period.*

COVID-19 pandemic. The rate per year increased from 26 to 36 patients. The rate also increased in the 2 types of acute leukaemia, AML and ALL, although the difference was not statistically significant. One possible explanation is that, as hypothesised, the COVID-19 pandemic impacted the immune system and immunosurveillance, thereby increasing the cancer risk. This would need to be confirmed by future studies and different types of neoplasia should be studied. The other possibility to explain the increase in rates is the earlier diagnosis, as patients and the healthcare system learned many lessons from the pandemic. According to the National Cancer Registry, the number of leukaemia cases increased from 91 in 2019 to 118 in 2020.[12] Unfortunately, this partly covers the present study period and includes all types of leukaemia. In addition, this study's data were obtained from a single centre. Sultan Qaboos University Hospital cares for approximately half of the patients diagnosed with acute leukaemia in Oman, while the other half is

Table 3: Characteristics before and during the COVID-19 pandemic of patients with acute myeloid leukaemia (n = 93)

Characteristic	n (%)*		P value
	During COVID-19	Before COVID-19	
Gender			0.99
Male	24 (52.1%)	25 (53.1%)	
Female	22 (47.8%)	22 (46.8%)	
Median finding			
Age in years (IQR)	40 (23–53)	45 (34–64.5)	0.05
Weight in kg (IQR)	68.2 (54.5–83.9)	70.5 (60.4–80.2)	0.55
Height in cm (IQR)	162.5 (153–170)	161 (152–164.5)	0.6
Haemoglobin in mg/dL (IQR)	8.1 (7.5–9.4)	8 (7.3–9)	0.68
white blood cells × 10^9/L (IQR)	6.9 (2.6–14.3)	8.9 (2.8–37.3)	0.19
Platelets × 10^9/L (IQR)	56 (33–163)	33.5 (23.5–84.2)	0.03
Lactate dehydrogenase in U/L (IQR)	371 (240–632)	377 (250.5–690.8)	0.27
Bone marrow blast per-centage (IQR)	59 (20.1–80.2)	70 (41.9–90.5)	0.08
NPM1			0.02
Positive	9 (20.9)	6 (16.7)	
Negative	34 (79.1)	30 (83.3)	
FLT3			0.67
Positive	11 (28.2)	9 (23.7)	
Negative	28 (71.8)	29 (76.3)	
PML_RARA			0.79
Positive	2 (11.8)	3 (18.8)	
Negative	15 (88.2)	13 (81.3)	
KMT2A			0.07
Positive	0 (0.0)	0 (0.0)	
Negative	7 (100)	16 (100)	
BCR_ABL1			0.04
Positive	0 (0.0)	1 (6.7)	
Negative	5 (100)	14 (93.3)	
ECOG performance status			
0	4 (8.6)	0 (0.0)	
1	20 (43.4)	32 (68.1)	
2	22 (47.8)	15 (31.9)	
3	0 (0.0)	0 (0.0)	
Central nervous system disease			0.26
Present	4 (8.7)	9 (19.1)	
Absent	42 (91.3)	38 (80.9)	
COVID-19 detection			
Detected	16 (34.8)	4 (8.5)	
Not detected	30 (65.2)	43 (91.5)	
Bone marrow trans-plant			
Transplanted	16 (34.8)	15 (31.9)	
Not transplanted	30 (65.2)	32 (68.1)	

IQR = interquartile range; ECOG = electrocorticography.

**The COVID-19 test status refers to COVID-19 infection at any time during the study's follow-up period*

cared for by the Royal Hospital. Finally, patients may have found travelling abroad for diagnosis and therapy challenging and chose to seek local medical care.

Although the difference between the outcomes of the pre-pandemic and pandemic periods was not statistically significant, the overall survival rates in 1 year were better for the COVID-19 period, especially in patients with ALL. This may not only reflect the possible earlier diagnosis discussed above but also be related to the non-direct impact of COVID-19. In this study, no significant difference was observed in the baseline characteristics between the two groups

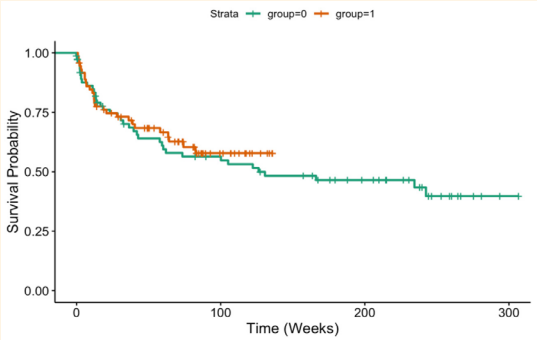

Figure 2: Overall survival of all patients with acute leukaemia during before (group 0) and during (group 1) the COVID-19 pandemic. The difference was not statistically significant ($P = 0.7$).

except for platelets. The last possibility to discuss is a difference related to chance, and with larger studies, the difference may not persist. This, again, needs to be confirmed in larger studies in different populations. By analysing the demographic data, this study did not identify significant differences in the male-to-female ratio compared to previous publications.[7–9] However, it is worth noting that the median age observed in this study was lower than the median age reported in earlier reports.[7–9]

Other factors may have changed the outcomes of patients during the pandemic. Telemedicine during the initial part of the pandemic was limited due to the limited infrastructure for this service. However, it has been increasingly used after the pandemic, and the regulations and infrastructure related to it are being improved. The care of patients with COVID-19, especially those with acute leukaemia and bone marrow transplantation, also plays a major impact on overall survival.[13] Another factor is vaccinations; patients with haematological malignancies were considered a priority group for the vaccinations, and this may have protected them from COVID-19 morbidity and mortality.

Diabetes mellitus was the most prevalent condition comorbidity among this study cohort, affecting 27 cases (17.9%) followed by smoking (n = 8, 5.3%). Compared to a systematic review that examined comorbidities and mortality rates in COVID-19 patients with haematological malignancies, hypertension was reported as the most prevalent comorbidity (44.6% of cases), followed by dyslipidaemia (32.1% of cases).[9] Furthermore, this study did not find significant differences in the prevalence of comorbidities between the pre-pandemic and pandemic periods, suggesting that the pandemic did not introduce significant changes in the prevalence of comorbidities among patients with acute leukaemia in the study population.

From a disease profile perspective, more NPM1-mutated AML (20.9%) were diagnosed during the pandemic compared to (17.6%) in the pre-pandemic period. The difference was not statistically significant, which may be related to the small sample size, small difference or chance. The higher proportion of NPM1, if a true observation, may explain the trend seen in the outcomes. Between the 2 periods, no other differences were found in the molecular or cytogenetic markers tested in this study. All of these observations need to be confirmed in larger studies.

This study observed a decrease in the median bone marrow blast percentage of AML patients during the COVID-19 pandemic (59% versus 70%; $P = 0.08$). This may indicate an earlier diagnosis of patients with acute leukaemia after COVID-19 and partially explain the better outcomes of these patients after the onset of the pandemic. It is known that COVID-19 affects the bone marrow and that there is an association between thrombocytopaenia in COVID-19 infection and outcomes in COVID-19.[14]

The major strength of this study is that it is the first to test the long-term immunological impact of COVID-19 on cancer immunosurveillance and the risk of developing cancer, in addition to the changes

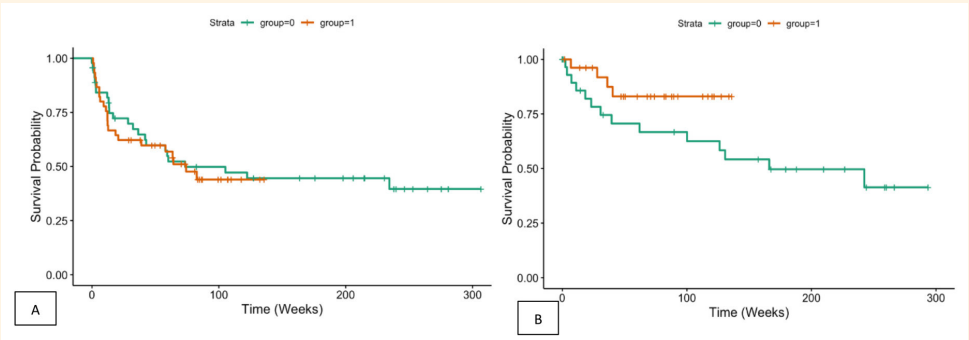

Figure 3: Overall survival of patients with (**A**) acute myeloid leukaemia and (**B**) acute lymphoblastic leukaemia before (group 0) and during (group 1) the COVID-19 pandemic. The differences were not statistically significant ($P = 0.7$ and $P = 0.1$, respectively).

in the clinical or laboratory characteristics of patients with acute leukaemia. However, this study has a small sample size and low power. Another limitation is that it is a single academic centre study. Additionally, some of the conclusions in this study are based on trends that are not statistically significant. Therefore, the findings from this study need to be confirmed in larger multicentre studies.

Conclusion

This study did not find statistically significant differences in the complete remission rates and overall survival of patients with acute leukaemia before and during the COVID-19 pandemic. However, considering the study's limitations, it is important to interpret these findings cautiously. Larger and multicentre studies are needed to confirm these findings.

AUTHORS' CONTRIBUTION

AAK contributed to the study design, data collection and manuscript drafting. TAB carried out data interpretation and manuscript review and correction. YAK performed data collection and manuscript review. FAB, MAH and MAB performed data interpretation and manuscript review and correction. MAK contributed to the study design, analysis, manuscript review and correction. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

No funding was received for this study.

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