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IDH1 and *IDH2* Gene Mutations in Omani Patients with Acute Myeloid Leukemia: Prognostic Significance and Clinic-pathologic Features

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ABSTRACT

Objectives: We sought to define the prevalence of isocitrate dehydrogenase (IDH) mutations, evaluate the clinicopathologic impact of IDH mutations, assess the effect of IDH mutations on the response to the currently offered treatment for acute myeloid leukemia (AML) cases, and determine the impact of other common concurrent mutations with IDH. ***Methods***: A single-center retrospective cohort study was conducted at Sultan Qaboos University Hospital (SQUH) from October 2009 to October 2019. We included all Omani patients (pediatric and adult) treated at SQUH with the standard therapy, for whom DNA extraction was performed at diagnosis. The target mutations in both *IDH1* and *IDH2* genes were screened using the direct polymerase chain reaction product sequencing method. Statistical analysis was conducted using SPSS software. Survival differences were estimated using the log-rank test. Continuous variables were presented as median (IQRs), while categorical variables were presented as frequency. ***Results:*** A total of 61 patients treated, for whom DNA extraction was performed at diagnosis were evaluated. The median age was 40 (range = 25.5–65.5). The prevalence of IDH1 R132, IDH2 R140, and IDH2 R172 mutations among the study group was 6.6%, 3.3%, and 1.6%, respectively. Clinicopathologic characteristics associated with IDH mutations at diagnosis included older age, lower white blood cell count, higher median platelet counts, normal karyotype AML, and cytogenetics intermediate-risk group. The overall survival (OS) in patients harboring IDH mutations was poor, with a median OS of nine months. This analysis confirms that the response rate and OS for both IDH-mutated and IDH wild-type AML patients were comparable. This will provide contemporary data to be used for comparison with the results of novel investigational (e.g., selective IDH inhibitor) strategies. ***Conclusions:*** The current study results were consistent with the other international studies of IDH mutations in AML and demonstrate the poor prognosis associated with IDH mutations. Clinicopathologic features associated with IDH mutations included older age, lower white blood cell count, higher median platelet counts, normal karyotype AML, and cytogenetics intermediate-risk group.

Myeloid leukemia is a heterogeneous group of diseases characterized by infiltration of the blood, bone marrow, and other tissues by neoplastic cells of the hematopoietic system.[1] In 2022, 20 050 new cases of acute myeloid leukemia (AML) were estimated in the USA.[2] Data demonstrated an association of myeloid leukemia with irradiation, smoking, some rare congenital abnormalities, chemical exposure, and obesity.[3]

According to the World Health Organization classification of hematological malignancies, recurrent genetic abnormalities were identified in AML. These genetic abnormalities are associated with distinctive clinicopathological features and have prognostic significance. The Cancer Genome Atlas Research Network evaluation of 200 AML cases found an average of 13 mutations per AML case, with at least 23 recurrent mutations identified. The most common identified mutations are FLT3, NPM1, CEBPA, cKIT, NRAS, MLL, WT1, IDH1/2, TET2, DNMT3A, and ASXL1.

In recent years, the analysis of whole genome led to the identification of two mutually exclusive mutations

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in isocitrate dehydrogenase *IDH1* genes: *IDH1* in the cytoplasm and *IDH2* in the mitochondria.[4,5]

After the discovery of IDH1 and IDH2, various studies were conducted to evaluate the prevalence of these mutations and their clinical and prognostic impact. Three main loci were studied: IDH1R132, IDH2R140, and IDH2R172.

Studies reported IDH mutations in around 33% of patients, including 6–16% for IDH1 and 8–19% for IDH2 mutations.[6–8] Five missense mutations were found in IDH1, including R132H, R132C, R132S, R132G, and R132V. IDH1R132 mutation was associated with other concurrent mutations including NPM1, FLT3, CEBPA, and NRAS.[9] Moreover, IDH2 mutations were found in 10.4%, with two missense mutations detected: R140Q and R172K.[10]

IDH mutation has a significant association with old age and higher median platelet counts, normal karyotype AML, cytogenetics intermediate-risk group, and NPM1 and FLT3-ITD mutations.[6,7,11,12] IDH1 mutation status is an unfavorable prognostic factor[11] and patients harboring IDH mutations have a significantly lower rate of five-year overall survival (OS) of 15.6% than patients who lack the IDH mutation (32.0%).[7]

The remission rates by AML treatment status were reported as 68% during induction, 42% in Salvage-1 (S1), and 27% in Salvage-2 and beyond (S21).[12] In addition, no difference in response identified by IDH mutation status was found.[12]

All the previous studies have addressed the impact and clinicopathological features of IDH mutations in AML patients conducted internationally, and no local studies are available. In addition to the common gene mutations detected frequently in AML patients such as NPM1, FLT3, and others where analysis at hematology department at Sultan Qaboos University Hospital (SQUH), the *IDH* gene mutation testing will serve as an additional important diagnostic molecular marker in Omani patients with AML. To fill the gap, our study aimed to estimate the prevalence of IDH mutations among Omani patients diagnosed with AML and the common types of IDH mutation will be identified and correlated with the clinical and laboratory findings.

METHODS

This single-center retrospective cohort study was conducted in SQUH. We used archived DNA collected from October 2009 to October 2019. The clinical data of the study population were obtained from the hospital information system. This research was ethically approved by the Institutional Review Board (IRB) at SQU (MREC #2048) and confidentiality was protected.

We included all Omani patients (pediatric and adult) treated at SQUH who were diagnosed with AML and had diagnostic DNA available for testing. All other patients who have missing data or their DNA extraction done at relapse or for other diagnosis (i.e., myelodysplastic syndrome) were excluded from the study.

The following hematological parameters have been assessed in all patients; full blood count including hemoglobin, hematocrit, white blood cells (WBC), and platelets count. Additionally, blood film smear, bone marrow aspirate, karyotyping, and DNA-based genetic studies were evaluated.

For IDH1 and IDH2 mutations detection, genomic DNA was extracted from EDTA-anticoagulated whole blood using the QIAamp DNA blood mini kit (Qiagen Inc, Hilden, Germany). The concentration and quality of the sample DNA were checked by NanoDrop ND-1000 (Nano-Drop Technologies, Wilmington, USA). The target regions for *IDH1* and *IDH2* genes were polymerase chain reaction amplified and directly sequenced using 3500 Genetic Analyzer. FLT3-ITD and NPM1 mutations were screened by capillary electrophoresis as described before.

Statistical analysis was conducted using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Kaplan-Meier method and the log-rank test were utilized to estimate the distribution of OS, with a p-value of < 0.05 was considered statistically significant. Continuous variables were presented as median (IQRs), while categorical variables such as French American-British classification and cytogenetics were presented as frequency.

RESULTS

We analyzed a total of 61 patients with AML, with a median age of 40 years. The baseline characteristics of the study population are summarized in Table 1.

Out of all tested AML cases, 54 (88.5%) had no IDH mutations (IDH1/IDH2 wild-type AML), while seven (11.5%) harbored either an IDH1 or an

Table 1: Patient demographic features (N = 61).

Parameters	n (%)
Age at diagnosis, median (IQR), years	40 (25.5–65.5)
Gender	
Male	31 (50.8)
Female	30 (49.2)
Hemoglobin, median (IQR), g/dL	8.3 (7.4–9.8)
WBC, median (IQR), 10^9/L	9.8 (2.9–53.8)
PLT count, median (IQR), 10^9/L	35 (23–99)
Blast %, median (IQR)	77 (52.3–87.2)
LDH, median (IQR)	394 (266–857)
Flow cytometry results	
APML	10 (16.4)
AML	46 (75.4)
Mixed phenotype	5 (8.2)
Risk stratification	
Favorable prognosis	8 (13.1)
Intermediate risk	17 (27.9)
High risk	35 (57.4)
Study group status	
Alive	17 (27.9)
Died	38 (62.3)
No records/lost to follow-up	6 (9.8)

WBC: white blood cell; PLT: platelet; LDH: lactate dehydrogenase; APML: acute promyelocytic leukaemia; AML: acute myeloid leukemia.

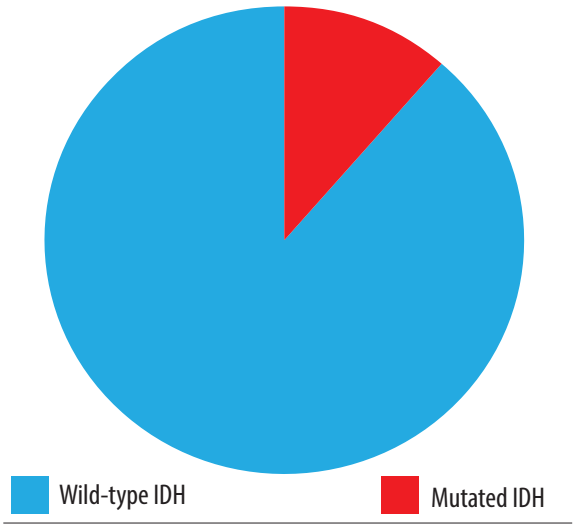

Figure 1: Percentage of IDH mutations.

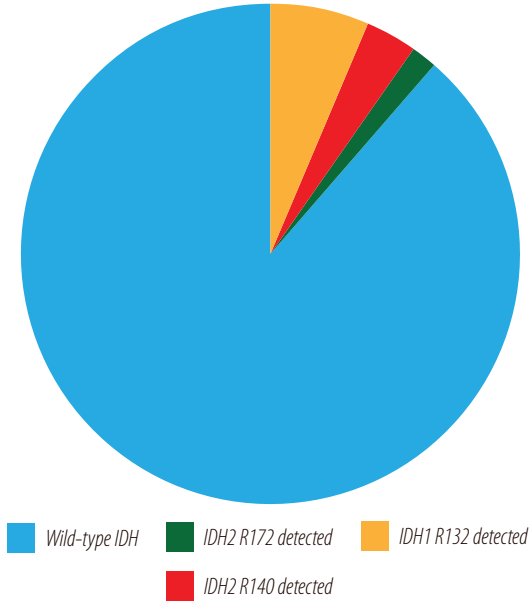

Figure 2: Loci of IDH1/IDH2 mutations detected.

IDH2 mutation [Figure 1]. Among all tested AML patients, an IDH1 mutation was detected in four (6.6%) cases, and an IDH2 mutation was detected in three cases (4.9%). The main loci identified in IDH1 mutation were p.R132C in three cases (75.0%) and p.R132H in one case (25.0%). For IDH2 mutation, p.R140Q and p.R172K were detected in 3.3% and 1.6%, respectively [Figure 2]. No cases had mutations in both IDH1 and IDH2, suggesting that these mutations are mutually exclusive.

The median age of the wild-type group was 37 years, whereas the median age for the mutated IDH group was 56 years. The female-to-male ratio in the IDH mutated group was 2.5:1. The mutated IDH group tended to have a lower WBC with a median of 4.4 × 10^9/L (1–37 × 10^9/L) and a higher platelet count with a median of 47 × 10^9/L (32–138 × 10^9/L) at diagnosis. There was no difference in hemoglobin levels between the two groups, with a median of 8.3 g/dL for the wild-type IDH and 7.9 g/dL for the mutated IDH group. Patient characteristics of both the wild-type and mutated IDH are displayed in Table 2.

The median blast count in the mutated IDH group was 81% (63–90%) whereas in the wild-type IDH group, it was 77.0% (51.5–85.7%). All the cases in the mutated group were classified as AML not otherwise specified based on World Health Organization AML classification. These cases were further classified using French American-British classification into AML without maturation (M1) in one patient (14.3%), AML with maturation (M2) in one patient (14.3%), acute promyelocytic leukemia variant (M3-v) in one patient (14.3%), acute myelomonocytic leukemia (M4) in two patients (28.6%), and acute monocytic leukemia (M5) in two patients (28.6%). Dysplastic features were described

Table 2: Comparison of patient demographic features between the study subgroups.

Parameters	IDH mutation negative (n = 55)	IDH mutation positive (n = 7)
Age at diagnosis, median (IQR), years	37 (18–61)	56 (42 – 70)
Gender, n (%)		
Male	29 (52.7)	2 (28.5)
Female	26 (47.3)	5 (71.4)
Hemoglobin, median (IQR), g/dL	8.3 (7.5–9.9)	7.9 (6.9–8.3)
WBC, median (IQR), 10^9/L	10 (3–59)	4.4 (1–37)
PLT count, median (IQR), 10^9/L	32 (23–94)	47 (32–138)
Blast %, median (IQR)	77.0 (51.5–85.7)	81 (63–90)
LDH, median (IQR)	406 (270–876)	266 (215–427)
Flow cytometry results, n (%)		
APML	10 (18.2)	0 (0.0)
AML	40 (72.7)	7 (100)
Mixed phenotype	5 (9.1)	0 (0.0)
Risk stratification, n (%)		
Favorable prognosis	8 (14.8)	0 (0.0)
Intermediate risk	12 (22.2)	7 (100)
High risk	34 (63.0)	0 (0.0)
Study group status, n (%)		
Alive	17 (30.9)	1 (14.3)
Died	34 (61.8)	4 (57.1)
No records/ lost follow-up	4 (7.3)	2 (28.6)

WBC: white blood cell; PLT: platelet; LDH: lactate dehydrogenase; APML: acute promyelocytic leukaemia; AML: acute myeloid leukemia.

in four patients (57.1%) with mutated IDH. These dysplastic features were identified mainly in granulocytes in one patient (14.3%), megakaryocytes in two patients (28.6%), and erythroid lineages in one patient (14.3%) [Table 3].

Among the studied AML patients, favorable, intermediate, and adverse cytogenetic risk was found in eight (13.1%), 17 (27.9%), and 35 (57.4%) cases, respectively. In the mutated group, two (28.6%) AML cases had normal karyotype, while five cases (71.4%) exhibited various cytogenetic abnormalities including trisomy 4, trisomy 11, trisomy 8, del (Y), and t(10,13) All IDH mutated cases (100%) were in the intermediate-risk cytogenetics group. Furthermore, 14.3% (one patient) in the IDH mutated group displayed concurrent mutations of both IDH1 and NPM1 [Table 4]. Unfortunately, the assessment of associations with other molecular abnormalities was hindered by the small sample size.

The median OS for the IDH1 and IDH2 mutated groups was nine months ($p = 0.593$). The estimated OS in the study cohort did not significantly differ between IDH wild-type and mutated IDH [Figure 3].

Table 3: Cytogenetic and molecular features of AML with *IDH1*^{R132}, *IDH2*^{R140}, and *IDH2*^{R172} mutations.

Age/ sex	FAB	Karyotype	Cyto-risk group	Mutation	Nucleotide change	A.A change	Other mutations (FLT3-ITD, NPM1)
74/F	M4	N. karyotype	Intermediate	*IDH1*	CGT-TGT	p.R132C	NPM1-, FLT3-ITD-
73/F	M1	+4	Intermediate	*IDH1*	CGT-TGT	p.R132C	NPM1+, FLT3-ITD-
56/M	M5	+11	Intermediate	*IDH1*	CGT-TGT	p.R132C	NPM1-, FLT3-ITD-
36/M	M5	-Y	Intermediate	*IDH1*	CGT-TGT	p.R132H	NPM1-, FLT3-ITD-
70/F	M2	T(10;17)	Intermediate	*IDH2*	CCG-CAG	p.R140Q	NPM1-, FLT3-ITD-
48/F	M2	N. karyotype	Intermediate	*IDH2*	CCG-CAG	p.R140Q	NPM1-, FLT3-ITD-
43/F	M4	+8	Intermediate	*IDH2*	AGG-AAG	p.R172K	NPM1-, FLT3-ITD-

AML: acute myeloid leukemia; IDH, isocitrate dehydrogenase; F: female; M: male; N: normal. FAB: French-American-British classification of AML.

Table 4: Hematologic and morphologic features of AML with IDH1^{R132}, IDH2^{R140}, and IDH2^{R172} mutations.

Pt. No	Mutation	Age/sex	FAB	WBC	Hb	PLT	Blast %	Auer Rods	Dysplastic features
1	IDH1	74/F	M4	3	10.1	138	31	++	Myeloid, Megas
2	IDH1	73/F	M1	91	8.3	338	81	-	Megas
3	IDH1	56/M	M5	1	7.2	32	79	?	?
4	IDH1	36/M	M5	8	5.9	14	63	-	Absent
5	IDH2	70/F	M2	4	7.9	47	90	-	Absent
6	IDH2	48/F	M2	37	6.9	35	95	++	Absent
7	IDH2	43/F	M4	1	8.3	132	88	-	Erythroid

AML: acute myeloid leukemia; IDH, isocitrate dehydrogenase. FAB: French-American-British classification of AML. WBC: white blood cell; Hb: hemoglobin; PLT: platelet; F: female; M: male. Case 3: Bone marrow aspiration not done as the patient refused.

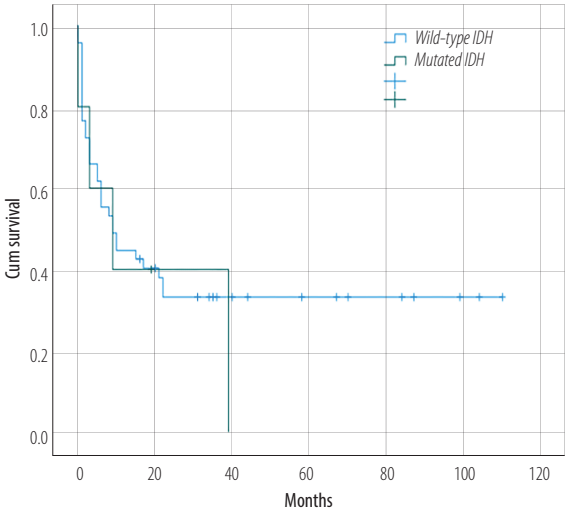

Figure 3: Overall survival between wild-type IDH and mutated IDH.

DISCUSSION

IDH mutations have been identified in a variety of malignancies, including gliomas,[14] chondrosarcomas,[15] cholangiocarcinomas,[6] and breast carcinomas.[7] Furthermore, these mutations have been found in myeloid neoplasms such as AML, myelodysplastic syndrome, and myeloproliferative neoplasms.[3] The normal function of IDH enzymes, encoded by *IDH* genes, is to convert isocitrate to α-ketoglutarate. Whereas mutant IDH enzymes, reduce α-ketoglutarate to its oncometabolite 2-hydroxyglutarate. The later inhibits α-ketoglutarate-dependent enzymes such as TET2. This results in abnormal epigenetic modifications that hinder cell differentiation.[8]

In our retrospective study, the overall frequency of IDH mutations among AML patients was 11.5%, which is lower than the reported incidence ranging from 16% to 33%.[4,5,13,16,17] This difference could be attributed to the extremely small sample size compared to other published studies. In our subgroup analysis of IDH mutations, IDH1 mutation was detected in four patients (6.6%) with the three main loci IDH1R132C (75.0%) and IDH1R132H (25.0%). Whereas IDH2 mutation was found in 4.9% of cases, with the main loci IDH2R140Q (3.3%) and IDH2R172K (1.6%). The reported incidence of IDH1 mutation ranges from 6–14% of cases while IDH2 is 8–19%.[4,5,13,16,17] Hence, the incidence rates of IDH1 and IDH2 mutation were consistent with international studies.

Our study revealed that patients with IDH mutations tended to be older, with a female predominance. The median age of mutated IDH patients reported in other studies ranged from 49 to 67 years.[11,16–18] Patel et al,[18] reported a male-to-female ratio of 1:3 whereas Green et al,[11] reported a ratio of 1:2. A lower median white cell count with higher median platelet count and blast percentage were observed in IDH mutated patients at diagnosis, which is consistent with other published international studies.[5,16,17] In agreement with other studies,[5,18,19] all mutated IDH cases were associated with intermediate cytogenetics risk. Chotirat et al,[17] identified 55% (11 cases) and 50% (12 cases) normal karyotype in mutated IDH1 and IDH2, respectively. In addition, they reported various cytogenetics abnormalities in aberrant karyotype including del(9q), trisomy 8, trisomy 11, del(12) (p12.1p13.1), t(15,17), and t(8;21). However, in this study, only 28.6% (two patients) has normal karyotype, one in each group. The identified cytogenetics abnormalities include trisomy 4, trisomy 11, trisomy 8, del (Y) and t(10,17). Furthermore, multiple studies were conducted to assess the concurrent presence of other gene mutations along with IDH mutation.

Table 5: Comparison of results between our study and other international results for patients with isocitrate dehydrogenase 1 (IDH1).

Variables	This study (n = 4)	Mardis et al, 2009 (n = 16)	Chou et al, 2010 (n = 27)	Marcucci et al, 2010 (n = 49)	Wagner et al, 2010 (n = 30)
IDH1	4/61	16/188	27/493	49/358	30/275
Age, years	61.5	48.9	52.5	62	50
(Mean, range)	(43.5–70.1)		(25–75)	(21–82)	(33–80)
Female:male	3:1	1.3:1	1.1:1	1:1.1	1:1.7
% Blast (mean, range)	80 (55–91.5)	76.7 ± 16.4	NA	73 (33–99)	80 (20–99)
Risk stratification, n (%)				NA	NA
Favorable	0 (0.0)	0	0		
Intermediate	4 (100)	16 (100)	26/26 (100)		
High risk	0 (0.0)	0	0		
IDH1 mutation, n (%)					
R132H	1 (25.0)	7 (44.0)	7 (26.0)	24 (49.0)	21 (70.0)
R132C	3 (75.0)	8 (50.0)	10 (37.0)	15 (31.0)	5 (17.0)
R132S	-	1 (6.0)	5 (19.0)	5 (10.0)	3 (10.0)
R132L	-	-	1 (4.0)	-	-
R132G	-	-	4 (15.0)	-	1 (3.0)
Coexisting mutations, n (%)					
NPM1	1 (25.0)	7 (44.0)	15 (56.0)	34 (71.0)	17 (57.0)
FLT3-ITD	-	4 (25.0)	10 (37.0)	10 (20.0)	4 (13.0)
CEBPA	-	NA	1(4.0)	2 (6.0)	8 (27.0)

***Meta-analysis data extracted from acute myeloid leukemia with IDH1 or IDH2 Mutations: Frequency and Clinicopathologic Features study, Am J Clin Pathol. 2011 Jan; 135 (1): 35-45.*

Patel et al,[18] reported the following additional gene mutations including *NPM1, FLT3-ITD, CEBPA, NRAS, KIT,* and *FLT3-D835 in IDH1*-mutated cases. A significant association between NPM1 and mutated IDH1 (74%; $p < 0.001$) and IDH2 (60%; $p < 0.001$) was demonstrated by Green et al.[11] We found concurrent presence of NPM1 mutation in one case with mutated IDH1. Unfortunately, our study's small sample size prevented a comprehensive assessment of such associations. Table 5 compares our results with other international studies.

In the context of OS, our study did not find a statistically significant impact of IDH mutations on survival compared to wild-type IDH. However, the small sample size may have limited our ability to detect a significant difference. This study represents the first effort to investigate the prognostic significance of IDH mutations in AML patients in Oman. Nonetheless, the study has several limitations, including its observational, retrospective nature, single-center design, and a limited number of AML patients with IDH mutations. The effectiveness of the current therapy to clear such mutation could not be assessed due to the short survival of patients. Future studies with larger sample sizes from multiple centers (including Royal Hospital and Oman's National Genetics Center) may provide more robust insights into the prognostic implications of IDH mutations and their response to therapy.

CONCLUSION

Our study revealed that the overall frequency of IDH mutations among AML patients in our cohort was 11.5%, with IDH1 mutations accounting for 6.6% and IDH2 mutations for 4.9%. Patients with IDH mutations tended to be older in age, exhibit a lower median WBC, higher median platelet count, and a higher blast percentage at diagnosis. Additionally, mutated IDH was associated with the intermediate cytogenetic risk group. However, we did not find a significant prognostic impact of IDH mutations on survival between the study groups. Considering these findings and the availability of new, targeted therapies for IDH mutations, we recommend implementing testing for IDH mutations as a primary diagnostic test for all newly diagnosed AML cases. This approach could facilitate

more personalized treatment strategies, taking into account the specific molecular characteristics of each patient's disease.

Disclosure
The authors declared no conflicts of interest. No funding was received for this study.

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