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Acute myeloid leukaemia in the Johannesburg public sector: A laboratory-based study

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Background: Acute myeloid leukaemia (AML) is a haematological malignancy stratified into low, intermediate and high-risk groups according to the genetic abnormalities present at diagnosis. Data relating to the epidemiology and outcomes of AML in Africa is sparse.

Aim: This study aimed to assess the AML risk profile, selected clinico-pathological features and follow-up of AML in Johannesburg.

Setting: The Johannesburg state sector.

Methods: All new cases of AML diagnosed on flow cytometry at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over 42 months between 2016 and 2019 were retrospectively identified. Clinical and laboratory data were obtained from the laboratory information system.

Results: A total of 277 AMLs were identified, with a median age of 37.5 years. Conclusive risk-stratification was possible in 183 patients, with the low-risk group predominating (51.9%). The distribution of high, intermediate and low-risk cases was similar between the adults < 60 years of age and the children < 15 years, while high-risk disease was significantly more common among older adults. High-risk disease was associated with lower long-term survival rates in younger adults and children, while outcomes appeared universally poor in older adults (irrespective of risk status). Early drop-off was common in low-risk disease, with an unexpectedly high rate of relapse in some low-risk entities.

Conclusion: Low-risk AML predominates in the Johannesburg state sector, but outcomes appear guarded. Exploration of measures to reduce sepsis-related mortality and further study of differences in local disease biology are required.

Contribution: This study contributes to the limited body of knowledge of AML in South Africa.

Keywords: acute myeloid leukaemia; low- and middle-income country; South Africa; acute myeloid leukaemia subtypes; European Leukaemia Net risk profile.

Introduction

Acute myeloid leukaemia (AML) is a haematological malignancy that is characterised by the accumulation of blasts within the bone marrow and/or blood. Normal haematopoiesis is progressively displaced by the blast population with ensuing features of bone marrow failure (infections, symptomatic anaemia and platelet pattern bleeding). Acute myeloid leukaemia predominates in the elderly with a median age of 65–70 years in high-income countries.[1,2]

The leading AML prognostic classification system among adults is the 2022 European Leukaemia Net (ELN) guideline,[3] which incorporates the results from conventional cytogenetics (CCy), fluorescence in situ hybridisation (FISH), polymerase chain reaction (PCR) and next-generation sequencing (NGS), to stratify patients into favourable, intermediate or adverse-risk groups according to the genetic abnormalities identified (Table 1). In children, there are slight differences in risk stratification as per the recommendations of the International BFM Study Group AML Committee.[4] Dissimilarities include the assignment of cases with FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutations into the adverse-risk group (as opposed to the intermediate-risk group in the ELN guideline), inclusion of acute promyelocytic leukaemia with PML::RARa (APL) as a favourable-risk entity (which is not included in the ELN classification because of its unique treatment), and the recognition of some mutations and translocations, which are rare in adults (Table 1). The expected favourable outcomes of the low-risk entities may be attenuated by the presence of accompanying mutations, such as *FLT3*-ITD in APL or *KIT* mutations in AML with *RUNX1::RUNX1T1* (*t*(8;21)), aberrant CD56 expression (in APL and *t*(8;21)),

TABLE 1: Acute myeloid leukaemia genetic risk classification systems in adults and children.

Risk status	Genetic abnormality
2022 European Leukaemia Net (ELN) guideline[3] used in adults	
Favourable	• *t*(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
	• inv(16)(p13.1q22) or *t*(16;16)(p13.1;q22)/*CBFB*::*MYH11*
	• Mutated *NPM1*, without *FLT3*- ITD or adverse risk cytogenetics
	• bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*, with *FLT3*-ITD
	• Wild-type *NPM1* with *FLT3*-ITD
	• *t*(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
	• Other cytogenetic or molecular abnormalities not otherwise classified
Adverse	• Complex karyotype (≥ 3 unrelated chromosome abnormalities) or monosomal karyotype†
	• −5 or del(5q); −7; −17/abn(17p)
	• *KMT2A*-rearranged (other than *t*(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A)*
	• *t*(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	• inv(3)(q21.3q26.2) or *t*(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)*
	• *t*(3q26.2;v)/*MECOM*(*EVI1*)-rearranged
	• *t*(6;9)(p23.3;q34.1)/*DEK*::*NUP214*
	• *t*(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP*
	• Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*
	• Mutated *TP53*
International BFM Study Group AML Committee risk classification system used in children[4]	
Favourable	• *t*(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
	• inv(16)(p13.1q22) or *t*(16;16)(p13.1;q22)/*CBFB*::*MYH11*
	• *t*(15;17) (q22;q21)/*PML-RARA*
	• Mutated *NPM1*
	• Biallelic *CEBPA* mutations
	• ***t*(1;11) (q21:q23)/*MLL-MLLT11(AF1Q)***
	• ***GATA1s* mutations**
Intermediate	• Mutated *NPM1*, with *FLT3-ITD*
	• Wild-type *NPM1* with *FLT3-ITD*
	• *t*(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
	• Other cytogenetic or molecular abnormalities not otherwise classified
Adverse	• Complex karyotype (≥ 3 unrelated chromosome abnormalities)
	• −5 or del(5q); −7
	• ***t*(4;11) (q21;q23)/*MLL-MLLT2(AF4)***
	• ***t*(6;11) (q27;q23)/*MLL-MLLT(AF6)***
	• ***t*(5;11) (q35;p15.5)/*NUP98-NSD1***
	• ***t*(10;11) (p12;q23)/*MLL-MLLT10(AF10)***
	• *t*(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	• inv(3)(q21.3q26.2) or *t*(3;3)(q21.3;q26.2)/*RPN1-MECOM(EVI1-MDS1-EAP)*
	• *t*(6;9)(p23.3;q34.1)/*DEK*::*NUP21*
	• Mutated ***WT1/FLT3-ITD***

NPM1, Nucleophosmin; *FLT3*-ITD, fms-like tyrosine kinase 3 internal tandem duplication; bZIP, basic leucine zipper domain; *CEBPA*, CCAAT enhancer binding protein alpha; *GATA1*, GATA Binding Protein 1; WT1, Wilms Tumour protein; AML, Acute myeloid leukaemia.

†, Monosomal karyotype: two or more monosomies (excluding loss of X or Y), or one autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML). Major differences with the ELN classification are shown in bold in the paediatric classification system.

secondary cytogenetic lesions (e.g. trisomy 8 and 22 in inv(16)) or a poor post-induction therapy response.[5,6,7,8,9,10] Furthermore, the risk associated with the various entities is based on optimal intensive therapy, and may not be as relevant where access to novel agents is limited. For example, *FLT3*-ITD mutations are now considered of intermediate-risk in the latest ELN guideline in part because of the superior outcomes seen in patients treated with a *FLT3* inhibitor (such as midostaurin).[3] Acute promyelocytic leukaemia is rendered curable through the use of various combinations of all-trans retinoic acid (ATRA), chemotherapy, arsenic trioxide and gemtuzumab ozogamicin, while the other favourable-risk AML subtypes have good survival rates when treated with intensive consolidation chemotherapy.[11] In contrast, adult patients with intermediate- or high-risk AML who are fit for intensive treatment should ideally be treated with allogeneic haemopoietic stem cell transplantation (HSCT) from an HLA-matched donor after induction chemotherapy.[12] In children, the role of HSCT is less clear, particularly in intermediate-risk disease.[13,14]

Data relating to the epidemiology and outcomes of AML in Africa is sparse, with the published literature being confined to aspects of the mutational profile in cytogenetically normal AML (CN-AML) and clinico-pathological features of APL.[15,16,17,18,19,20] These studies have suggested a younger median patient age among South Africans with AML, a higher prevalence of APL, and differences in the mutational profile in CN-AML compared to those reported in high-income countries. In this study, we aimed to assess the diagnostic classification, disease risk profile, selected clinico-pathological features and crude outcomes of AML diagnosed in the state sector laboratories in Johannesburg, South Africa (SA).

Methods

Study design

We retrospectively retrieved all cases of newly diagnosed acute leukaemia recorded in the patient register at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) flow cytometry unit over 42 months between 2016 and 2019. This laboratory provides immunophenotyping services to all southern Gauteng region state sector hospitals. The laboratory information system (LIS) was then used to obtain demographic information, clinical history (when provided), haematological results (full blood count, differential count, bone marrow aspirate and trephine biopsy), immunophenotypic information (flow cytometry, immunohistochemistry), virology, microbiology and chemistry results, as well as CCy, FISH, and PCR results. Cases subsequently classified as representing blastic transformation of underlying chronic myeloid leukaemia or a myeloproliferative neoplasm were excluded. Cases were classified according to the World Health Organization (WHO) classification of Haematopoietic and Lymphoid Neoplasms (5th edition, 2022).[21] Since mutational analysis for *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* and *TP53* was not performed in our laboratory during the study period, classification according to these mutations was not possible. Cases were risk-stratified according to the ELN 2022 classification system or International BFM Study Group AML Committee as appropriate, and in APL, disease risk was further stratified according to the Sanz risk score.[22] The latter incorporates the presentation white cell count (WCC) (> or < 10×10^9/L) and platelet count (> or < 40×10^9/L) to assign

high (WCC > 10), intermediate (WCC ≤ 10, platelets ≤ 40) or low-risk (WCC ≤ 10, platelets > 40) status. We defined complete remission (CR) as the absence of morphological disease or a population of cells with the leukaemia-associated immunophenotype on low-sensitivity flow cytometry (FACS Calibur instrument [BD Biosciences, San Jose, California, United States of America], sensitivity ~0.1%) and the absence of recurrent genetic abnormality on FISH analysis (Abbott, Chicago, Ilinois, United States [US]) or CCy.

Statistical analysis was performed using Prism software, version 5 (GraphPad Software, San Diego, California, US). Skewed numerical data were described using medians with interquartile ranges (IQRs), and categorical data using frequencies (percentages). The two-sample Wilcoxon rank-sum (Mann-Whitney) was used to compare skewed continuous data. Fisher's exact test was used to compare categorical data, and Spearman correlation was used to assess for significant relationships between variables of interest. The time period that blood tests were registered for a patient on the LIS at a tertiary referral centre, namely the Chris Hani Baragwanath Academic Hospital (CHBAH) or the CMJAH – served as a surrogate measure of survival. Although imprecise, this information is a valid indicator of survival because there is minimal use of state oncology facilities by patients with medical aid in Johannesburg, and patients are strictly treated in the facility corresponding to their residential address. As a result, there is negligible movement of patients to alternative oncology facilities. Furthermore, the treatment of AML requires intensive laboratory monitoring, and all laboratory tests are submitted to the National Health Laboratory Services laboratories at these sites. The laboratory record therefore gives a fair reflection of the patients' clinical course. Patients in peripheral hospitals with no further work-up after the diagnostic investigations were excluded from this analysis, as it could not be certain whether they were referred elsewhere or had demised. Mortality related to sepsis was considered likely in patients with positive blood cultures for pathogenic organisms and/or very high C-reactive protein (CRP) levels together with severe neutropenia (neutrophils < 0.5×10^9/L), with or without renal failure or a coagulopathy, and whose laboratory record ceased abruptly without evidence of recovery. The very early and early drop-off rates were calculated as the proportion of patients who had blood results available for less than 7 and 30 days, respectively. A two-sided *p*-value of 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the University of the Witwatersrand Human Ethics committee (protocol no. M150160). Patient consent was not a requirement as the study was a retrospective analysis of laboratory results obtained from the laboratory information system (LIS) (Trackcare, Intersystems, Cambridge, Massachusetts, United States). Patient identifying information was stored in a password-protected Excel spreadsheet with unique study numbers providing the link to patient results.

TABLE 2: Pertinent demographic and laboratory information.

Parameter	Result				
	n	*N*	%	Median	IQR
Age (years)	-	-	-	37.5	17–58
• Children (< 15 years)	-	-	-	5.5	1.8–10
• Adults (15–59 years)	-	-	-	47	30–63
Male	-	143	51.6	-	-
Female	-	134	48.4	-	-
HIV seropositive	31	186	16.7	-	-
Risk Stratification†				-	-
• Low risk	95	183	51.9	-	-
• Intermediate risk	39	183	21.3	-	-
• High risk *n*/*N*(%)	49	183	26.8	-	-
White cell count ($\times 10^9$/L)	-	-	-	17.8	5.3–69
Haemoglobin (g/dL)	-	-	-	6.7	5.1–8.3
Platelets ($\times 10^9$/L)	-	-	-	33	16–63
Neutrophils ($\times 10^9$/L)	-	-	-	1.35	0.28–5.01
Peripheral blood blasts (%)	-	-	-	58	30–83
Hyperleukocytosis (White cell count > 150 × 10^9/L)	26	273	9.5	-	-
Complete remission	49	84	48.3	-	-
12-month follow-up rate	37	205	18.0	-	-
• Children (< 15 years)	18	50	36.0	-	-
• Adults (15–59 years)	17	107	15.8	-	-
• Older adults (≥ 60 years)	2	48	4.2	-	-

†, As per the ELN guidelines in adults and the International BFM Study Group AML Committee in children.

Results

A total of 277 new cases of AML were diagnosed on flow cytometry in the reviewed period, comprising 60.1% of all cases of acute leukaemia (*n* = 461). Pertinent demographic and laboratory information is summarised in Table 2. The cohort's median age was 37.5 years (IQR: 17–58.3), with 64 cases (23.1%) seen in children under 15 years of age and 64 (23.1%) in older adults (≥ 60 years). The human immunodeficiency virus (HIV) status was available in 186 patients (67.1%), with an HIV-seropositivity rate of 16.7%. Most of the patients living with HIV (*n* = 25/31, 80.6%) were adults between 15 and 59 years of age, with only two children and four adults aged 60 years or older testing HIV-positive.

Definitive diagnostic classification was not possible in 87 cases owing to the absence of comprehensive molecular data (PCR, CCy and/or FISH results). A karyotype was successfully performed in 160 (57.8%) cases and was normal in 49 (30.6%). Among the classifiable cases, the most common WHO subtype diagnosed was APL (22.6%), followed by myelodysplasia-related AML (AML-MR) (21.5%) and AML with *t*(8;21) (16.6%) (Table 3). There were substantial differences in the distribution of cases according to age, with APL predominating in children and younger adults, and AML-MR making up close to half of the classifiable cases among older adults (Figure 1). Notably, KMT2A gene-rearrangements occurred predominantly in the children, while *nucleophosmin (NPM1)* mutations were seen with increasing frequency with increasing age. Acute myeloid

TABLE 3: Classification of cases according to the World Health Organization classification of haematopoietic and lymphoid neoplasms (5th edition, 2022).

WHO subtype	Proportion of all cases (*n* = 277)		Proportion of classifiable cases (*n* = 190)		Proportion of paediatric cases (*n* = 52)		Proportion of adult cases (*n* = 138)		Proportion of elderly adult cases (*n* = 30)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Acute myeloid leukaemia (AML) with defining genetic abnormalities	145	52.3	145	76.3	39	75.0	106	76.8	22	73.3
• Acute promyelocytic leukaemia with *PML::RARa* fusion (APL)	43	15.5	43	22.6	12	23.1	31	22.5	1	3.3
• AML with *RUNX1::RUNX1T1* fusion (*t*(8;21))	32	11.6	32	16.8	8	15.4	24	17.4	2	6.6
• AML with *CBFB::MYH11* fusion (inv(16))	4	1.4	4	2.1	1	1.9	3	2.2	0	0
• AML with *RBM15::MRTFA* fusion (*t*(1;22))	2	0.7	2	1.0	2	3.8	0	0	0	0
• AML with *KMT2A* rearrangement	10	3.6	10	5.3	6	11.5	4	2.9	0	0
• AML with *MECOM* rearrangement	1	0.4	1	0.5	0	0	1	0.7	1	3.3
• AML, myelodysplasia-related	40	14.4	40	21.5	7	13.5	33	23.9	14	46.7
• AML with *NPM1* mutation	13	4.7	13	6.8	3	5.8	10	7.2	4	13.3
AML, defined by differentiation	26	9.4	26	13.7	5	9.6	21	15.2	3	10.0
• AML with minimal differentiation	3	1.1	3	1.6	0	0	3	2.2	1	3.3
• AML without maturation	6	2.2	6	3.2	0	0	6	4.3	0	0
• AML with maturation	6	2.2	6	3.2	2	3.8	4	2.9	1	3.3
• Acute myelomonocytic leukaemia	5	1.8	5	2.6	2	3.8	3	2.2	0	0
• Acute monocytic leukaemia	5	1.8	5	2.6	0	0	5	3.6	1	3.3
• Acute erythroid leukaemia	1	0.4	1	0.5	1	1.9	0	0	0	0
• Acute megakaryoblastic leukaemia	0	0	0	0	0	0	0	0	0	0
Secondary myeloid neoplasms	19	6.9	19	10.0	10	19.2	9	6.5	5	16.7
• Myeloid neoplasm post-cytotoxic therapy	9	3.2	9	4.7	0	0	9	6.5	5	16.7
• Myeloid neoplasm associated with germline predisposition	10	3.6	10	5.3	10	19.2	0	0	0	0
○ Down Syndrome	8	2.9	8	4.2	8	15.4	0	0	0	0
○ Bone marrow failure syndromes (Fanconi anaemia)	2	0.7	2	1.1	2	3.8	0	0	0	0

leukaemia with inv(16) was distinctly uncommon in all age groups.

Post-induction therapy-response assessment was available in 94 patients (33.9%), of whom 54 (57.4%) achieved CR, with or without complete recovery of the blood counts. The majority (*n* = 150/183 [82%]) of patients without a remission assessment were traceable for less than 1 month, 26 (14.2%) had no post-induction bone marrow performed, and 7 (3.8%) had an inadequate or inconclusive post-induction bone marrow. Follow-up (crude survival) data were available in 205 patients (74%), with a median follow-up period of 1.75 months (IQR 0.5–8.75) and only 37 (18%) still actively followed up beyond 12 months after diagnosis. Very short follow-up times (< 7 days) occurred in 34 patients (16.6%), most commonly affecting those with APL, AML with KMT2A-rearrangements and AML with *NPM*1 (Figure 2). The presence of hyperleukocytosis (WCC >150 × 10^9/L) was significantly associated with very early drop-off (r_s = 0.25, p = 0.001), and was most commonly seen among patients with AML with KMT2A (33.3%) and AML with *NPM1* (30.8%) (Table 4).

Acute promyelocytic leukaemia occurred at a median age of 24 years (IQR: 12–36), with only one case seen in an older adult, where it was suspected to represent AML secondary to previous cytotoxic therapy for breast carcinoma. The majority of cases had high-risk Sanz scores (22/43 [51.2%]), with low-risk scores seen in only four cases (9.3%). Just over one third of morphologically classified cases (13/36) were microgranular variants, with high rates of *FLT3*-ITD mutations in these patients (Table 4). The median follow-up time of APL was only 1.5 months (IQR: 0.1–26.5), with a large proportion of patients followed up for less than 7 (10/32, [31.3%]) and 30 days (*n* = 15/32 [46.9%]), respectively. Post-induction bone marrow analysis results were available in 15 patients, only 9 (60%) of whom had achieved CR. There was no association between remission status and microgranular morphology, *FLT3*-mutation status, aberrant CD56 expression or the presence of additional abnormalities on CCy. Among the patients in CR post-induction, one out of nine (11.1%) subsequently relapsed. The 12-month follow-up rate was 34.4% and among the 16 patients who were documented to have survived for more than 1 month, 11 (68.8%) were followed up beyond a year. Further noteworthy laboratory data are summarised in Table 4.

Acute myeloid leukaemia myelodysplasia-related occurred at a median age of 54 years (IQR: 31.3–65) and was defined by the presence of MDS-defining cytogenetic abnormalities in the majority (38/40 [95%]) of cases. Post-induction remission assessment was available in 10 patients, with only one (10.0%) achieving a complete remission. The median LIS follow-up period among these patients was 1.3 months (IQR: 0.4–4.9), with a 12-month crude survival rate of only 2.8%. The median follow-up time did not differ significantly between the adults (1 month, IQR: 0.3–3) and the children (4.5 months [IQR: 0.6–9.3], p = 0.19), with none of the children (0%) and only one of the adults (3.3%) surviving

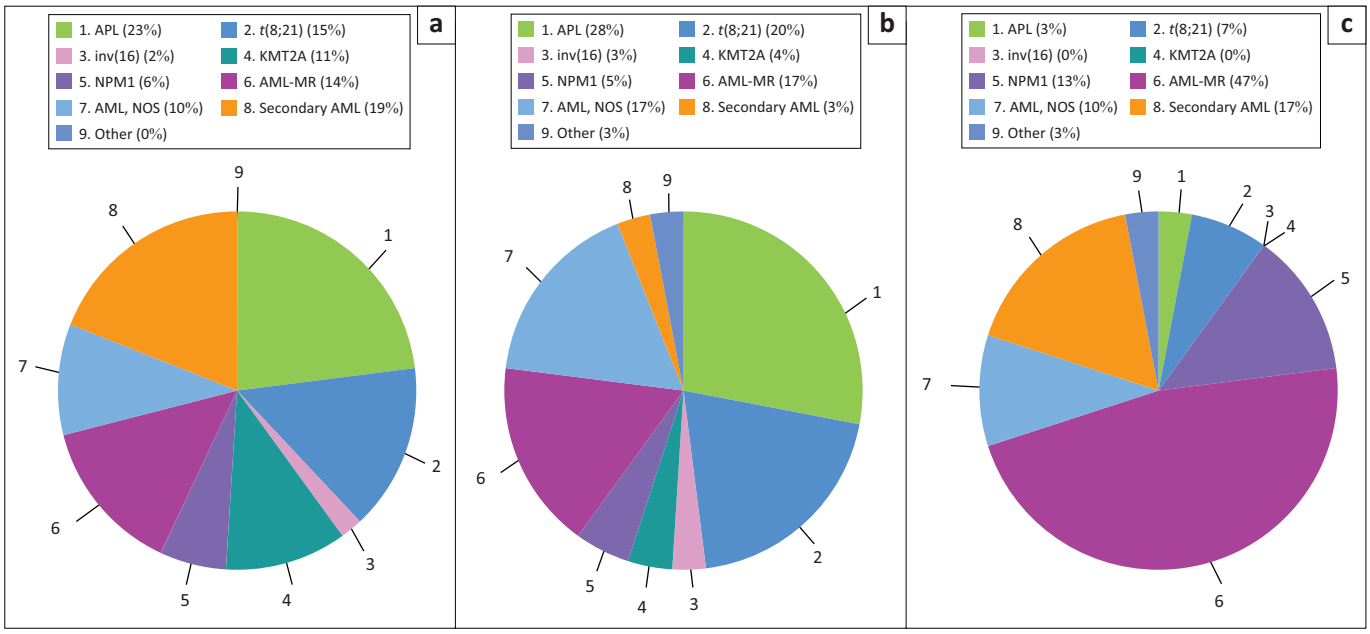


FIGURE 1: Distribution of classifiable cases according to age (a) children (< 15 years), (b) adults (15–59 years) and (c) older adults (≥ 60 years).

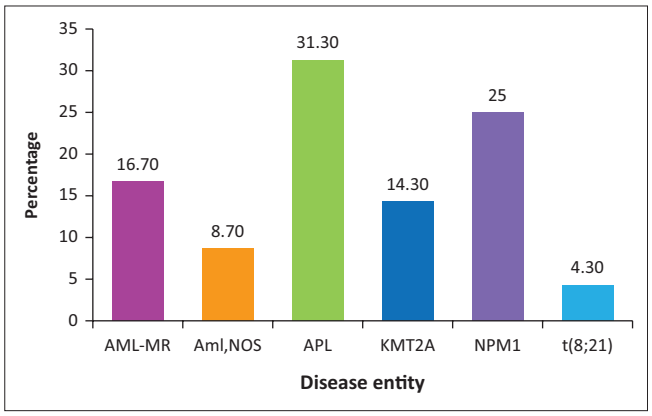


FIGURE 2: Proportion of cases with very early drop-off (< 7 days).

beyond 12 months. Further noteworthy laboratory data are summarised in Table 4.

Acute myeloid leukaemia with *t*(8;21) occurred at a median age of 28.5 years (IQR: 15.3–41) and had the longest median follow-up time seen in this cohort (5 months [IQR: 0.7–22.3]), with a 12-month follow-up rate of 30.8% and the lowest very early drop-off rate (4.3%) (Figure 2). While most cases were morphologically classified as AML with maturation (as is typical for this entity), approximately one third of patients (9/28) were not (Table 4). Post-induction remission assessment was performed in 21 patients, and 17 (81%) achieved CR. Despite this, four of the patients in CR post-induction (23.5%) later relapsed. The median follow-up times were significantly longer among the children with *t*(8;21) as compared to the adults (33 months [IQR: 16.9–39] versus 2.5 months [IQR: 0.6–8.9], $p = 0.006$). Additional karyotypic abnormalities were present in 12 of the 25 patients with a karyotype available, with loss of the Y-chromosome being the most common additional abnormality detected (present in 5 of the 12 males tested). The median follow-up time appeared shorter in the patients with additional cytogenetic abnormalities (5.3 months [IQR: 0.5–12.5] vs. 12 months [IQR: 0.7–36]), but this difference lacked statistical significance ($p = 0.27$). Further noteworthy laboratory data are summarised in Table 4.

Cytogenetically normal AML occurred at a median age of 40 years (IQR: 22–61 years) and had a 12-month follow-up rate of 14.3%. Of the 20 patients with post-induction bone marrow results, 10 (50%) were not in remission. *NPM1* mutations were detected in 26.9% (7/26) of patients and *FLT3*-ITD mutations in 23.1% (6/26) (Table 4). The WCC was notably exceptionally high in cases with *NPM1* and concurrent *FLT3*-ITD mutations (Table 4). The median follow-up time in the patients with *NPM1* mutations was only 1 month (IQR: 0.2–31), with 25% (3/12) of patients followed up for less than 1 week. The latter represented one of the highest very early drop-off rates in this cohort (Figure 2). This may have been attributable to complications of hyperleukocytosis (WCC > 150 × 10^9/L), which was present in two of the three patients with *NPM1* mutations who dropped-off within 7 days. The follow-up periods appeared longer in cases without concomitant *FLT3*-ITD mutations (4 months vs. 2 weeks in *FLT3*-ITD positive case) and among children as compared to adults (31 months vs. 0.9 months), but these findings lacked statistical significance ($p = 0.55$ and 0.06, respectively), possibly because of the small sample size ($n = 12$). Of the patients with post-induction assessment performed, 3/6 (50%) were in CR, but among the five patients who were documented to have survived for more than 1 month, 4 (80%) were followed up beyond a year. Further noteworthy laboratory data are summarised in Table 4.

Disease risk stratification was possible in 183 patients, with the low-risk group comprising the largest subgroup (51.9%) (Table 2). There was no significant difference in the distribution of high, intermediate or low-risk cases between

TABLE 4: Detailed laboratory features of the most common acute myeloid leukaemia subtypes.

Laboratory feature	Acute promyelocytic leukaemia (APL)	AML with *t*(8;21)	Cytogenetically normal AML	AML with KMT2A	AML-myelodysplasia-related (AML-MR)	AML defined by differentiation
WCC (× 10^9/L) median (IQR)	10.8 (4.5–34.0) • Microgranular: 32.2 (6.5–71.1) • Hypergranular: 6.6 (1.5–15.5)	22.2 (13.1–59.4)	41.9 (7.6–107.0) • *NPM1*+: 54 (29.5–199.6) • *NPM1*+*FLT3*-ITD+: 213 (IQR 193–214)) • *NPM1*+*FLT3-ITD*-:38.9 (IQR 23.6–54.8) • *NPM1*-*FLT3*-ITD+: 29.3 (IQR 2.8–77.8	78.9 (2.4–256.9)	11 (3.0–36.3)	19.8 (7.5–9.1)
Hyperleukocytosis (WCC >150 × 10^9/L) *n*/*N* (%)	3/43 (7) • Microgranular: 1/13 (7.7) • Hypergranular: 0/22 (0)	0/34 (0)	5/43 (11.6) • *NPM1*+*FLT3*-ITD: 4/4 (100) • *NPM1*+*FLT3*-ITD-: 0/9 (0) • *FLT3-ITD*+NPM1-: 0/4 (0)	3/9 (33.3)	2/40 (5)	3/26 (11.5)
Subgroups defined on PCR *n*/*N* (%)	• *FLT3*-ITD PCR+: 4/14 (32.6). • *FLT3*-ITD PCR+ microgranular cases: 4/5 (80).	• *KIT* gene mutation analysis: performed in insufficient numbers for meaningful analysis	• *NPM1*+*FLT3*-ITD+: 2/26 (7.7) • *NPM1*+*FLT3*-ITD-: 5/26 (19.2) • *FLT3*-ITD+*NPM1*-: 4/26 (15.4)	• None	• None	• None
Morphological characteristics *n*/*N* (%):	• Microgranular morphology: 13/35 (37.1).	• Morphological classification by differentiation: AML without maturation 4/28 (14.3) • AML with maturation 19/28 (67.9) • Acute myelomonocytic leukaemia 4/28 (14.3) • Acute monocytic leukaemia 1/28 (3.6).	• Morphological classification by differentiation of cases with *NPM1*: ○ AML without maturation 6/12 (50) ○ AML with maturation 2/12 (16.7) ○ Acute myelomonocytic leukaemia 3/12 (25) ○ Acute monocytic leukaemia 1/12 (8.3). • Morphological classification by differentiation of cases with *FLT3*-ITD (negative for *NPM1*): ○ AML with minimal differentiation 1/4 (25) ○ AML without maturation 1/4 (25) ○ Acute myelomonocytic leukaemia 1/4 (25) ○ Acute monocytic leukaemia 1/4 (25).	• Acute myelomonocytic leukaemia 2/9 (22.2) • Acute monocytic leukaemia 7/9 (77.8).	• Morphological classification by differentiation: • AML with minimal differentiation 4/31 (12.9) • AML without maturation 3/31 (9.7) • AML with maturation 15/31 (48.4) • Acute myelomonocytic leukaemia 5/31 (16.1) • Acute monocytic leukaemia 1/31 (3.2). • Acute megakaryoblastic Leukaemia 3/31 (9.7)	• Morphological classification by differentiation: • AML with minimal differentiation 3/26 (11.5) • AML without maturation 6/26 (23.1) • AML with maturation 6/26 (23.1) • Acute myelomonocytic leukaemia 5/26 (19.2) • Acute monocytic leukaemia 5/26 (19.2) • Acute erythroid leukaemia 1/26 (3.8)
Immunophenotypic peculiarities *n*/*N* (%):	• Aberrant expression of CD2 present: ○ Aberrant expression of CD2 in microgranular cases: 8/13 (61.5) ○ Aberrant expression of CD2 in hypergranular cases: 2/22 (9) ○ Aberrant expression of CD56: 7/16 (43.8)	• Aberrant expression of CD19: present in 20/30 (66.7) • Aberrant expression of CD56: present in 7/12 (58.3).	• AML with NPM1: ○ Blasts negative for CD34: 12/13 (92.3) ○ Blasts negative for HLA-DR: 8/13 (61.5)	• None	• Aberrant CD7 expression: 14/34 (41.2)	• None

Note: All numbers quoted refer to the number of cases tested/classified.

AML, acute myeloid leukaemia; WCC, white cell count; PCR, polymerase chain reaction.

the adults under 60 years of age and the children. However, significant differences in the frequency of low- and high-risk disease were seen among older adults (Figure 3). The median follow-up period did not differ significantly according to risk-status (median follow-up 2.5 [IQR: 0.5–22.5], 1.5 [0.4–6.7] and 1.5 [IQR: 0.3–5.6] months in the low-, intermediate- and high-risk groups, respectively). This was as a result of similarly high early drop-off rates within the first month across the risk categories (42.9% in high-risk, 35.1% in intermediate-risk and 36.4% in low-risk cases). However, there were notable differences in the proportion of cases with follow-up for at least 1 year according to risk status in the children and younger adults (< 60 years), while all of the older adults dropped off in less than 12 months, irrespective of risk status (Figure 4). No association was seen between the follow-up time and HIV

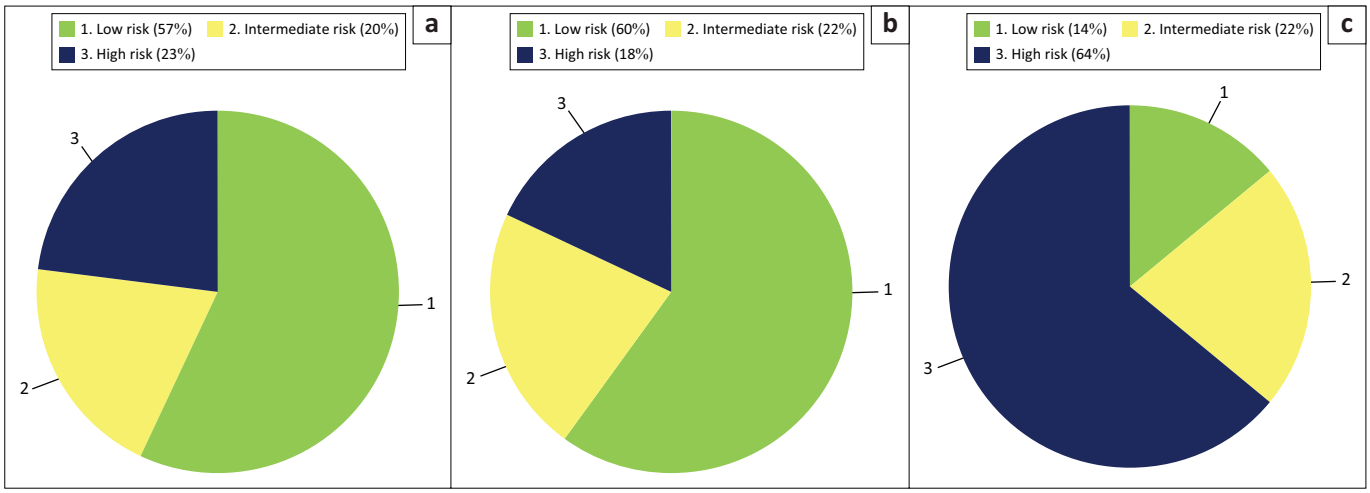


FIGURE 3: Disease risk stratification according to age (a) children (< 15 years), (b) adults (15–59 years) and (c) older adults (≥ 60 years).

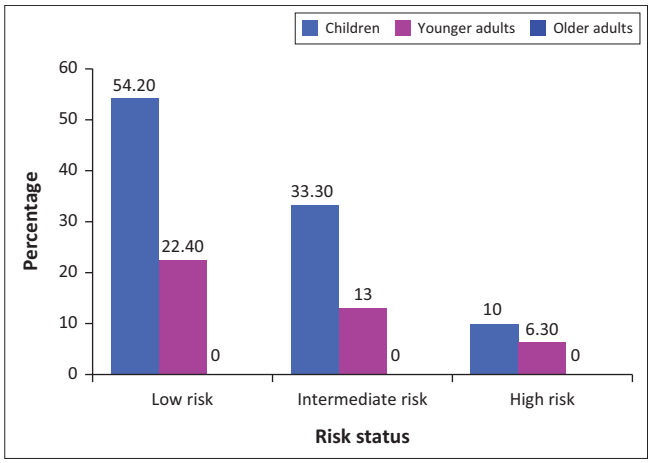


FIGURE 4: Twelve-month follow-up rates according to risk status and age.

status, but achievement of a CR post-induction chemotherapy was significantly linked to longer follow-up time (median follow-up 11 months [IQR: 4.4–31.3] vs. 4.8 months [IQR: 1.7–9.3] if not in remission, $p = 0.001$), as was a WCC < 50 × 10^9/L (median follow-up 2 months [IQR: 0.5–10] vs. 0.6 months [IQR: 0.1–4.5] if WCC > 50 × 10^9/L, $p = 0.002$). Sepsis appeared to be a significant contributor to mortality, with evidence of infection immediately preceding the cessation in laboratory results in 27/83 (32.5%) of those who dropped off within 1 month, and in 25/66 (37.9%) of those without evidence of relapsed/refractory leukaemia who dropped-off between 1 month and 1 year from diagnosis.

Discussion

This study has confirmed the very different disease distribution of AML in the South African setting compared to that seen in high-income countries. As reported in other low- and middle-income countries,[23,24,25,26,27] the median patient age was considerably younger than is typically seen in the developed world[1,2] and APL is substantially more common than the 5% – 8% of younger patients in high-income countries.[28] Also, as described elsewhere (both locally[18,20] and abroad[29,30,31]), high-risk APL was very common, and presumed early death rates were high. In addition, the rate of CN-AML was somewhat lower than the 40% – 50% cited in other parts of the world[32,33] (in line with other South African studies[15,16,17]), with a lower frequency of *NPM1* mutations (26.9% vs. 45% – 64% elsewhere). The latter concurred with a previous report from Johannesburg[17] (23.5%), but was considerably lower than the frequency reported in a study conducted in Cape Town (39.0%). Like APL, the frequency of AML with *t*(8;21) was substantially higher than that reported elsewhere (1% – 5%),[28], while AML with inv(16) was distinctly less so (5% – 8% among younger patients in high-income countries[28]). Collectively, these findings suggest regional differences in disease biology, both between SA and other parts of the world, as well as at a provincial level within SA.

Despite the dominance of seemingly low-risk disease, outcomes appeared overall poor in this study, with 12-month follow-up rates of 38.8%, 16.7% and 0% in the children, younger adults and older adults, respectively. These findings are in agreement with two unpublished studies from Johannesburg, which showed long-term survival rates of 6% and 32% in adult[34] and paediatric[35] patients, respectively, as compared to 5 year survival rates over 50% in patients < 40 years of age in high-income countries.[2] High-risk disease was associated with shorter follow-up times in the younger adults and children, while the older adults had extremely poor long-term survival, irrespective of risk status. The latter highlights the need for greater access to appropriate therapeutic options such as venetoclax and hypomethylating agents in this group, which are not routinely available in the Johannesburg state sector.

The low median follow-up time in low-risk patients was largely because of high early drop-off rates in patients with APL and AML with *NPM1*, possibly reflecting delays in patient referral and commencement of ATRA therapy for the former, and a significant contribution from hyperleukocytosis-related mortality to the latter. Importantly, long term follow-up rates were good among

patients with both APL and AML with *NPM1* who survived beyond the first month after diagnosis. A need for more intensive early support is clear. In addition, our findings suggest that sepsis-related mortality plays a considerable role in the poor outcomes seen, and the substantially poorer follow-up time seen in adults with AML with *t*(8;21) as compared to the children with this entity suggests that treatment among the adults may be insufficiently intense. Other factors likely curtailing survival in our setting include the extremely limited access to allogeneic stem cell transplantation in the Johannesburg state-sector, the generally poorer outcomes consistently reported among individuals of African descent[2] (who make up the majority of patients seen in our setting), and poor socioeconomic status, which was shown to have a significant bearing on outcomes of childhood cancer in another South African study.[36] Furthermore, the poor outcomes in AML with *NPM1* (irrespective of *FLT3*-ITD mutation status) and the occurrence of disease relapse in > 20% of AML with *t*(8;21) with a good response to induction chemotherapy raise the possibility of differences in disease biology in our setting, causing higher risk behaviour in seemingly low-risk disease. Similar poor outcomes have been described among African American patients with core binding factor AML (which includes AML with *t*(8;21)),[2] possibly reflecting differences in host pharmacogenomics or socioeconomic factors. Alternatively, this could be because of a higher rate of the presence of concurrent high-risk mutations in patients of African descent (such as *KIT* D816 mutations in AML with *t*(8;21) or *DNMT3A* mutations in AML with *NPM1*); further studies assessing the mutational landscape of these entities in our setting would be of interest. The high rate of relapse in patients with *t*(8;21) in CR post-induction also suggests the need to employ more sensitive methods of measurable residual disease assessment to improve risk stratification in our setting, particularly in patients with *t*(8;21).

Lastly, the high early drop-off and sepsis-related mortality rates in this study testify to the inadequacies of the state-sector healthcare system in Johannesburg, with staff and drug shortages, as well as insufficient access to intensive care facilities leaving patients with acute leukaemia vulnerable. Systematic improvement in the state-sector healthcare system, particularly with regard to intensive care capacity, would likely improve early mortality rates. Advocacy in this regard is needed. In addition, further investigation into measures to reduce the risk of neutropenic sepsis could potentially reduce mortality considerably in our setting. In particular, the use of granulocyte colony stimulating factor (G-CSF) therapy may be of value. This has been shown to reduce the duration of chemotherapy-associated neutropenia in patients with AML in high-income countries.[37,38,39] While this did not translate into a reduction in the number of infections or improvement in survival in other parts of the world, this strategy may prove to be of more value in the South African public sector setting, where support for neutropenic sepsis (such as intensive care access) is often limited. The benefit of reducing the duration of neutropenia in this setting may thus have a more significant impact on the rate of sepsis-related mortality.

Conclusion

Low-risk AML predominates in the Johannesburg state-sector, but outcomes are seemingly poor. Exploration of measures to improve early support and reduce sepsis-related mortality is required, as is advocacy for access to novel agents in older patients. Lastly, further study of local disease biology and employment of more sensitive disease monitoring could improve lococentric disease risk stratification.

Limitations

One of the major limitations of this study was the inability to sub-classify a significant number of AML cases because of patient demise before a complete work-up or the absence of a comprehensive molecular work-up. Because of this study's retrospective and laboratory-based design, the outcome data are also suboptimal, and requires further validation and correlation with the treatment given. In order to overcome some of these limitations, future studies should include review of patient files. This will limit the number of missing data sets and provide more comprehensive and accurate clinical, treatment and outcome data. Lastly, the lack of available testing for many of the mutations associated with high-risk disease in this study means that the rate of high-risk disease is likely underestimated here. Further study in this regard would be of interest.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

J.V. performed data collection, data analysis and wrote the article. K.H. performed data collection and provided editorial input.

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Data availability

The data that support the findings of this study are available from the corresponding author, J.V., upon reasonable request.

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