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Acute promyelocytic leukaemia: A central South African experience

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Background: Targeted therapies combined with anthracycline chemotherapy have improved the survival of patients with acute promyelocytic leukaemia (APL). High short-term mortality has been demonstrated in low- and upper-middle-income countries, with limited local data.

Aim: This study aimed to describe the demographic variables, clinical characteristics and laboratory features associated with the short-term mortality of patients with APL.

Setting: The Division of Clinical Haematology, Universitas Academic Hospital (UAH), Bloemfontein, South Africa.

Methods: Demographic and clinical data were obtained from the patients' files and the MEDITECH electronic filing system. Laboratory data were retrieved from TrakCare, the National Health Laboratory Service (NHLS) electronic database. Data were analysed to report the demographic variables, clinical characteristics and laboratory features, and the short-term mortality of all newly diagnosed patients treated for APL during the 5-year period, 2015–2019.

Results: Twenty-seven patients were included in this study. The 7-day mortality rate was 18.5%, and the 30-day mortality rate was 33.3%. Sanz and modified Sanz scores were significantly associated with 7-day mortality but not 30-day mortality. Creatinine ≥ 105 µmol/L was significantly associated with both 7- and 30-day mortalities. Patients who died within the first 30 days of admission had significantly higher median white cell counts and partial thromboplastin times. Hypogranular APL was identified in 55.6% of patients.

Conclusion: The short-term mortality of APL at UAH is in keeping with findings at other treatment centres in middle-income countries. Despite being considered rare, hypogranular APL was the predominant type in this cohort.

Contribution: This study highlights the need for practices pertaining to peripheral smear utility and interpretation to be reviewed outside of tertiary centres.

Keywords: acute promyelocytic leukaemia (APL); early mortality; hypogranular type; clinical findings; laboratory findings; early outcome; South Africa.

Introduction

Acute promyelocytic leukaemia (APL) is a subset of acute myeloid leukaemia (AML) that comprises a group of haematological malignancies involving precursors of the myeloid cell line.[1] According to the World Health Organization (WHO) classification of AML, APL is categorised under AML with recurrent genetic abnormalities, as APL with *PML-RARA*.[2,3] The cytogenetic and molecular profile of APL t(15;17)(q22;q12) is associated with a favourable prognosis.[2]

The pathogenesis of APL involves a translocation in the gene that encodes for the retinoic acid receptor on chromosome 17 (retinoic acid receptor alpha gene, *RARA*) and the promyelocytic leukaemia *(PML)* gene on chromosome 15, resulting in the *PML-RARA* fusion gene or t(15;17)(q22;q12).[4,5] This translocation accounts for up to 98% of cases of APL, with further rare variant translocations also described.[6,7]

Retinoic acid plays a key role in the terminal maturation of granulocyte precursors, a process mediated through the retinoic acid receptors (RAR), with the alpha isoform of the receptors being expressed predominantly in haematopoietic cells. The *PML-RARA* oncogene observed in APL encodes for the transcription of a hybrid protein that acts as an atypical receptor. Consequently, retinoic acid-induced differentiation of the myelocytes is impeded,[4,5] resulting in the accumulation

of granulocyte precursors (promyelocytes) in the peripheral blood and bone marrow.[3] These abnormal promyelocytes can evoke life-threatening haemorrhage resulting from disseminated intravascular coagulation (DIC) and hyperfibrinolysis.[8,9,10,11] Bleeding accounts for 32% – 64% of early deaths and is the major cause of treatment failure during induction.[9,12,13,14,15,16] Coagulopathy, necessitating prompt treatment and intensive management with blood products and referral to experienced treatment centres, has become the hallmark of APL.[17,18]

The increased availability of targeted therapies such as all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO), combined with anthracycline chemotherapy, has improved APL outcomes. Complete remission rates of 90% – 95%, long-term survival exceeding 75% and early death (defined as death during induction therapy) below 10% have been reported in large multi-centre trials.[9,12,13,19] Population-based studies have contradictory findings, with early death rates ranging between 17.3% and 29% in upper-middle to high-income countries. These studies defined early deaths as death occurring either within 14 or 30 days of diagnosis, respectively.[14,15,17,18,20] Similar findings in several institutional studies in low- and middle-income countries further highlight discrepancies and the need for ongoing population-based studies.[21,22,23]

The primary objective of the study was to describe the demographic variables, clinical characteristics and laboratory features that might have been associated with short-term (7-day and 30-day) mortality of patients with APL treated at the Division of Clinical Haematology at Universitas Academic Hospital (UAH), Bloemfontein, South Africa, during the period 2015–2019. The secondary objectives were to describe the treatment provided and the supportive care required during the first 30 days.

Methods

Study design

A retrospective, quantitative, cross-sectional study was performed.

Setting

The Division of Clinical Haematology is a sub-speciality public facility that treats patients from the Free State, Northern Cape and parts of the Eastern Cape provinces in South Africa, and Lesotho, a neighbouring country.

Patients

Patients were identified from the UAH institutional APL database and laboratory databases and from the electronic pharmacy records for patients who received ATRA at UAH. Consecutive files of all patients older than 13 years of age with APL, who had the first presentation during the study period (01 January 2015 – 31 December 2019), were included. The diagnosis of APL was based on morphologic features and molecular tests, including fluorescence in situ hybridisation (FISH) and polymerase chain reaction (PCR). Patients were excluded if they presented for follow-up, had relapsed disease, had variant translocations (other than t(15;17)), or if clinical and laboratory data could not be traced.

Data sources

The data collected were demographic variables, clinical and laboratory findings during the first 30 days of admission, and pharmacy and transfusion records. Demographic and clinical data were obtained from the patients' files and the MEDITECH electronic patient file system. Laboratory data were retrieved from TrakCare, the National Health Laboratory Service (NHLS) electronic database. No personal identifiers were captured.

Study data were collected and managed using REDCap (Research Electronic Data Capture),[24,25] hosted by the University of the Free State (UFS).

Quantitative variables

Full blood count (FBC), coagulation data and CD4 counts were collected as continuous variables. Age, various dates, creatinine clearance, baseline left ventricular ejection fraction (LVEF), number of units transfused (red cell concentrate, platelets, cryoprecipitate and fresh frozen plasma independently) and dose of dexamethasone were collected as discrete variables.

Sanz,[26] modified Sanz[27] and DIC scores[28,29,30] were calculated based on the results of collected laboratory variables. A positive FISH result was defined by the presence of the translocation t(15;17). A positive quantitative polymerase chain reaction (qPCR) was defined by the presence and quantity of t(15;17), *PML-RARA* fusion transcript copies. The 7- and 30-day mortalities were based on the first presentation to UAH.

Categorical variables

Patients were classified according to the peripheral smear morphological characteristics described by the WHO as having either hypogranular or hypergranular APL.[3] The granular type was assigned by the haematopathologist at the time of diagnosis and confirmed by a second haematopathologist. Gender, nationality, clinical features at presentation (bleeding sites, infection sites, comorbidities, HIV status and HIV viral load) and outcomes (neutropenic sepsis, differentiation syndrome, ICU admission, outcome and cause of death) were collected as categorical variables.

Statistical analysis

Data analysis was performed using Statistical Analysis Software (SAS), Version 9.4 (SAS Institute Inc.; Cary, NC, United States [US]). Numerical variables were expressed as medians (interquartile ranges [IQR]) and compared using the Kruskal–Wallis test. Categorical data were expressed as

percentages and compared using the chi-square or Fisher's exact test. The level of statistical significance was set at $p < 0.05$.

Ethical considerations

Approval to conduct this study was obtained from the UFS Health Sciences Research Ethics Committee (HSREC) (ethics approval number UFS-HSD2020/0448/3006) and the Free State Province Department of Health (approval number FS_202005_034). Signed informed consent was not required because of the retrospective nature of the study.

Results

Number of patient files

Fifty-three files were screened for eligibility, of which 27 were included in the study. Figure 1 summarises the patient files screened for eligibility and reasons for exclusions.

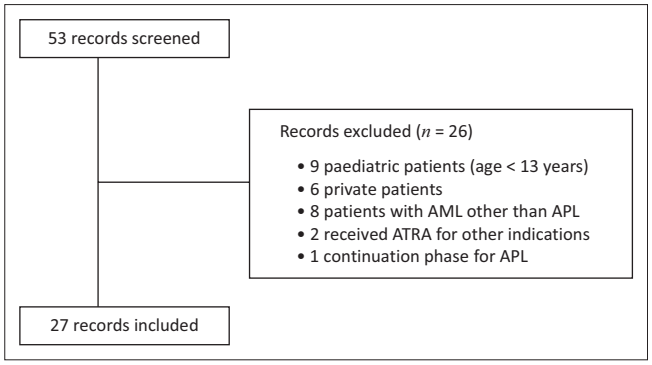
Demographic variables

The majority ($n = 22$; 81.5%) of the patients were South African citizens from the Free State ($n = 13$; 59.1%) and Northern Cape ($n = 8$; 36.4%) provinces. One South African patient (4.5%) was referred from the Eastern Cape, while the remainder were referred from Lesotho. A slight male predominance of 55.5% (male-to-female ratio of 1:0.8) was observed. The median age of the patients was 31.8 years (range 15–65 years).

Clinical features

Comorbidities were documented in over a third ($n = 10$; 37.0%) of the study population. Hypertension was most frequently reported, followed by human immunodeficiency virus (HIV) infection ($n = 6$ and $n = 3$, respectively). Other comorbidities (all $n = 1$) included previous pulmonary tuberculosis, diabetes mellitus, asthma, mitral valve prolapse and renal failure. Three patients had more than one comorbidity.

All patients were symptomatic on presentation to UAH, and slightly more than three-quarters ($n = 21$; 77.8%) had more than one symptom at presentation. The most frequently reported clinical feature was symptomatic anaemia ($n = 20$; 74.1%) followed by bleeding ($n = 18$; 66.7%) and infection ($n = 9$; 33.3%). Both bleeding and thrombotic complications were observed at presentation. Table 1 summarises the clinical features of the patients at presentation to UAH.



AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; ATRA, all-*trans* retinoic acid.

FIGURE 1: Selection of records included in the study.

Laboratory, molecular and genetic characteristics of patients

Full blood count

All patients had an FBC performed on admission. Table 2 summarises the baseline FBC findings.

Morphological findings

Hypogranular APL was the predominant morphological type among patients ($n = 15$; 55.6%), hypergranular APL occurred in 11 (40.7%) patients and the morphological type of one patient was unknown.

Coagulation studies

Coagulopathy screening was performed on all patients on admission. Table 2 summarises the coagulation study results. All patients fulfilled the International Society on Thrombosis and Haemostasis (ISTH) DIC criteria for overt DIC. However, clinical features supporting DIC were found in 21 patients (77.8%), most of whom had bleeding and a few had thrombotic features ($n = 18$; 85.7% and $n = 3$; 14.3%, respectively).

TABLE 1: Clinical features of patients with acute promyelocytic leukaemia at first presentation to Universitas Academic Hospital.

Clinical features at presentation	*n*	%
Symptomatic anaemia	20	74.1
Bleeding†	18	66.7
Source of bleeding		
Ecchymoses	5	27.8
Epistaxis	6	33.3
Gastrointestinal	3	16.7
Haematuria	1	5.6
Haemoptysis	0	0.0
Intracranial bleed	1	5.6
Menorrhagia	3	16.7
Minor mucocutaneous bleeds	3	16.7
Retinal bleed	2	11.1
Retroperitoneal bleed	0	0.0
Other (post-dental procedure)	1	5.6
Infection‡	9	33.3
Source of infection		
Lower respiratory tract infection	1	11.1
Cerebral abscess	1	11.1
Peri-anal infection	1	11.1
Skin and soft tissue infection	1	11.1
Upper respiratory tract infection	5	55.6
Urinary tract infection	1	11.1
Thrombosis	3	11.1
Site of thrombus		
Ischemic stroke	3	100.0
Venous thromboembolism	0	0.0
Other presenting features		
Decreased level of consciousness	2	7.4
Lymphadenopathy	3	11.1
Visual disturbance	3	4.4

†, Seven participants had more than one bleeding site at presentation; ‡, One participant had more than one infection site at presentation.

TABLE 2: Baseline full blood count results and coagulation studies of the cohort.

Investigation performed at baseline	Laboratory reference ranges	Median	IQR
Full blood count results			
Haemoglobin (g/dL)	-	6.7	5.7–8.2
White cell count (× 10^9/L)	-	10.8	2.4–50.2
Neutrophil count (× 10^9/L)	-	0.4	0.1–2.5
Platelet count (× 10^9/L)	-	16	12–28
Coagulation studies			
Prothrombin time (PT) (s)	9.9–12.3	16.3	15.5–17.5
Partial thromboplastin time (PTT) (s)	21.6–28.7	25.3	22.7–29.8
Fibrinogen (g/L)	-	1.7	1.2–2.7
D-dimer (mg/L)	0.00–0.25	15.7	8.2–24.0
ISTH DIC score	-	6	6–6

IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; DIC, disseminated intravascular coagulation.

Sanz score

Over half of the patients (n = 14; 51.9%) fell into the Sanz[26] high-risk group. In contrast, only one (3.7%) of the patients had a low-risk score, with the remaining 12 (44.4%) classified as intermediate-risk.

Modified Sanz score

When the modified Sanz[27] score was applied, approximately half of the patients (n = 14; 41.9%) were classified as high-risk patients and a quarter of the patients were classified as ultra-high-risk patients (n = 7; 25.9%). Intermediate-risk (n = 5; 18.5%) and low-risk (n = 1; 3.7%) patients accounted for less than a quarter of the total study population.

Genetic features

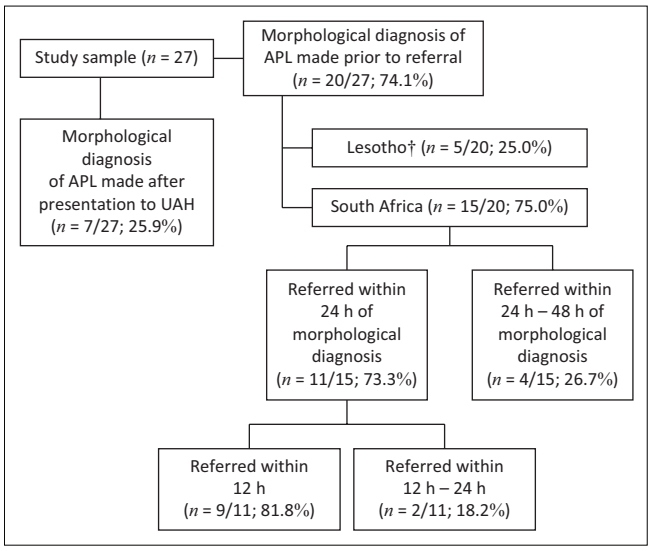
A diagnosis of APL was confirmed by FISH for t(15;17) in 26 (96.3%) cases and by *PML-RARA* reverse transcription-polymerase chain reaction (RT-PCR) in a single case. The median percentage of positive t(15;17) cells was 65% (IQR: 57% – 75%). A baseline qPCR for *PML-RARA* was requested for six (22.2%) patients, with a result being obtained in five (18.5%) cases. In one patient, the total ribonucleic acid (RNA) yield was insufficient to produce a result. Among those with a qPCR result, the median number of *PML-RARA* copies was 3277 (IQR: 1229–4273 copies).

Management of patients with acute promyelocytic leukaemia

The first suspicion of acute promyelocytic leukaemia and time to referral to Universitas Academic Hospital

Approximately three-quarters (n = 20; 74.1%) of the patients were referred to UAH with a clinical and laboratory suspicion of APL, while the remaining patients (n = 7; 25.9%) were referred with alternate diagnoses. All patients from Lesotho were referred with a presumed diagnosis of APL based on peripheral smear results.

The time and date of the first suspicion of APL, based on morphologically suggestive smear results, were known for all 22 South African patients, but unknown for the patients from Lesotho. In 15 (68.2%) South African patients, the morphological diagnosis was made prior to referral to UAH.



APL, acute promyelocytic leukaemia; UAH, Universitas Academic Hospital.

†, No data were available on the time and date of the first suspicion of APL for patients from Lesotho.

FIGURE 2: An illustration of the time taken for referral to Universitas Academic Hospital after a morphological diagnosis of acute promyelocytic leukaemia was made.

The median time (hours [h], minutes [min]) between the first morphological suspicion of APL and referral of South African patients to UAH was 9 h 32 min (IQR: 4 h 20 min to 24 h 21 min). Most South African patients with an APL diagnosis based on peripheral blood morphology prior to referral were presented to UAH within 24 h (n = 11/15; 73.3%), of whom nine (81.8%) were referred within 12 h (Figure 2). A delay of 46 h 12 min was reported for one patient, with delayed transportation documented as the cause. Figure 2 illustrates the various time intervals from the first suspicion of APL to referral to UAH.

Index presentation: Referral complications

In the context of this article, 'index presentation' refers to the date and time of the first FBC performed on a patient at the referring healthcare facility. In three patients, the index presentation was unknown, and for these cases, the documented date and time of the first presentation to a healthcare facility was used.

The median time (days) between index presentation and transfer to UAH was three days (IQR: 1–6 days). However, when a peripheral blood smear result accompanied the FBC at index presentation and APL was reported on the smear, a significantly shorter median time between presentation and referral to UAH was observed (p = 0.01). Table 3 summarises the time difference between index presentation and referral to UAH. Twelve patients had a peripheral smear done at index presentation at the referring facility. A further five patients did not have features of APL reported on the initial peripheral blood smear. However, abnormalities noted on the smear prompted further investigations, which led to the diagnosis of APL.

All seven patients who had an automated FBC and differential white cell count had abnormal FBC findings. Five patients

TABLE 3: Comparison of time to referral to Universitas Academic Hospital based on investigations performed at index presentation.

Investigation performed at index presentation	*n*	%	Time in days between index presentation to a healthcare facility and first presentation to UAH	
			Median	IQR
Peripheral smear with APL reported	12	44.4	1	0.5–1
Peripheral smear with APL not reported	5	18.5	12	5–17
Automated FBC with differential count†	7	25.9	5	43–6
Unknown	3	11.1	2	1–34

APL, acute promyelocytic leukaemia; FBC, full blood count; IQR, interquartile range; UAH, Universitas Academic Hospital.

†, In these cases, only an automated FBC was performed without a peripheral smear.

had pancytopenia, one patient had leucocytosis (white cell count 57.59 × 10^9/L) and one had both anaemia (haemoglobin 4.6 g/dL) and thrombocytopenia (platelet count 11 × 10^9/L). All seven patients subsequently had peripheral blood smear results suggestive of APL.

Management of patients at Universitas Academic Hospital

One patient's treatment file could not be traced, and another patient died prior to the commencement of treatment. The results pertaining to treatment in particular are reported for the remaining 25 patients. All other analyses included these two patients' information.

All 25 patients received ATRA according to their pharmacy records. The dates and times of the first dose of ATRA were known for 19 (76.0%) patients. In six patients (five from South Africa and one from Lesotho), the date of the first ATRA dose was unknown. Most patients from South Africa received the first ATRA dose within 24 h of a peripheral blood smear result confirming morphological features of APL (*n* = 13/15; 86.7%). Two patients received doses more than 24 h after the first suspicion of APL (47 h 28 min and > 48 h, respectively).

While patients from Lesotho all had peripheral blood smear results on which a morphology-based suspicion of APL was reported, the date and time of the smear results were not recorded. Considering the time from index presentation to the referring hospital and documented administration of the first ATRA dose, most patients from Lesotho (*n* = 3/5; 60.0%) received the first dose after 48 h (range: 4–9 days), and only one (20.0%) patient received the first ATRA dose within 24 h.

In 19 patients, ATRA was administered in the majority of patients (*n* = 14; 73.7%) before confirmation of APL with FISH or PCR, while five (26.3%) patients received ATRA immediately after the FISH/PCR results were available.

In addition to ATRA, all patients received chemotherapy with daunorubicin, an anthracycline. The median time (days) that chemotherapy commenced after the first presentation to UAH was one day (IQR: 1–2 days). The LVEF was quantified at baseline in most patients (*n* = 22; 88.0%). One patient had a low LVEF of 42% at baseline, requiring a daunorubicin dose reduction.

TABLE 4: Blood products administered to patients during the first 30 days of admission to Universitas Academic Hospital (*n* = 25).

Blood product	Patients that received blood product		Total number of units	Median	IQR
	n	%			
Red cell concentrate					
Leukodepleted	23	92.0	117	5	3–7
Non-leukodepleted	3	12.0	6	2	1–3
Platelets					
Apheresis	24	96.0	96	3	3–6
Pooled†	4	16.0	6	1.5	1–2
Fresh frozen plasma	9	36.0	66	8	3–10.5
Cryoprecipitate	10	20.0	212	16	9–21

IQR, interquartile range.

†, Pooled platelets comprise a pool of five buffy coats, non-leukodepleted, of a similar blood group.

Corticosteroids (dexamethasone) were prescribed to most patients (*n* = 20; 80.0%). The indications for dexamethasone were prophylaxis to prevent and treat differentiation syndrome (*n* = 20; 80.0% and *n* = 4; 20.0%, respectively). All patients with a white cell count above 10 × 10^9/L received dexamethasone according to treatment guidelines.[31,32,33]

Five (20.0%) patients required admission to the intensive care unit (ICU) within the first 30 days of hospitalisation. All patients required blood products. Table 4 describes the supportive treatment of patients in terms of blood products received during the first 30 days of admission.

Patients with a Sanz score in the high-risk category required more supportive care in terms of blood products (309 vs. 194 units) and ICU admissions (4 vs. 1). In contrast, the median number of red cell transfusions per patient was significantly higher (*P* = 0.01) in the intermediate-/low-risk Sanz score group than that in the high-risk group. There were no statistically significant differences between the high-risk and intermediate-/low-risk groups regarding the number of units of platelets, fresh frozen plasma and cryoprecipitate transfused (Table 5).

No statistically significant difference was observed between the groups' ICU admission rates and transfusion requirements using the modified Sanz score.

Complications reported in the first 30 days of admission

Cytopenia

All 27 patients had a nadir haemoglobin count below 8 g/dL (median: 5.4 g/dL, IQR: 4.6–5.9 g/dL). The median nadir platelet count during the first 30 days of admission was 8 × 10^9/L (IQR: 6–14 × 10^9/L), with a nadir platelet count below 10 × 10^9/L observed in more than half of the patients (*n* = 15; 55.6%). Neutropenia occurred in all patients, with a median nadir neutrophil count of 0.04 × 10^9/L (IQR: 0.01–0.22 × 10^9/L).

Neutropenic sepsis and differentiation syndrome

Neutropenic sepsis was reported in 19 (70.4%) patients. Differentiation syndrome occurred in four (14.8%) patients.

TABLE 5: Comparison of intensive care unit admissions and blood products received between the high-risk and non-high-risk groups based on the Sanz score.

Sanz score	High	Median	IQR	Intermediate/ low	Median	IQR	*p*
Total number of patients (*n* = 25)	13		-	12	-	-	-
Blood products (total units)	309	17	4–29	194	11	9–21	0.87
Patients that received blood products	13/13	-	-	12/12	-	-	-
Red blood cell concentrate	45	3	1–5.5	78	6.5	5.5–7	0.01
Patients transfused	11/13		-	12/12	-	-	-
Platelets	47	3	2–5	55	4	3–5	0.36
Patients transfused	12/13	-	-	12/12	-	-	-
Median (IQR)		-			-		
Fresh frozen plasma (FFP)	42	0	0–1	24	0	0–3.5	0.90
Patients transfused	5/13	-	-	4/12	-	-	-
Cryoprecipitate	175	9	0–18	37	0	0–2.5	0.10
Patients transfused	7/13	-	-	3/12	-	-	-
ICU admission	4/13	-	-	1/12	-	-	0.23

IQR, interquartile range; ICU, intensive care unit.

Short-term mortality

Two-thirds (*n* = 18; 66.7%) of patients were alive at 30 days, of which seven (38.9%) had a hospital stay of more than 30 days. The median admission time at UAH for patients that survived the first 30 days was 27 days (IQR: 24–51 days). A 100% (*n* = 5) mortality rate was observed among patients admitted to the ICU. The causes of death included intracranial haemorrhage (*n* = 2), ischemic stroke (*n* = 1), ischemic stroke with haemorrhagic transformation (*n* = 1), sepsis (*n* = 4), differentiation syndrome with sepsis (*n* = 1) and an unidentified cause (*n* = 1).

More than half (*n* = 5/9; 55.6%) of deaths occurred within the first seven days of admission to UAH. Ischemic and haemorrhagic complications were the cause of death in patients who died in the first seven days of admission (*n* = 4/9; 44.4% and one unknown). This finding was contrary to those who died after the first seven days, where sepsis and differentiation syndrome were documented as the cause of death (*n* = 4; 44.4%). Tables 6a and 6b summarise the association between various parameters and the 7- and 30-day mortality rates.

Discussion

Early mortality in APL remains a considerable challenge at UAH. As a referral and specialised haematology treatment centre, we would have expected our APL outcomes to be in line with other academic centres.[15,16] However, our mortality even exceeds the mortality of the Canadian Cancer Registry, which included all patients with APL managed at various centres and not only those managed at specialist referral centres.[15] This may be because of a delay in timely diagnosis and referral, although contrary to what has been shown in other South African centres.[16] A third of the patients in the cohort died within the first 30 days of presentation to UAH, with more than half of the deaths occurring within the first week. This observation was in keeping with the findings of institutional studies in other lower-middle and upper-middle-income countries,[21,22,23] although contrary to the results of large-scale clinical trials and population-based studies in high-income countries.[9,13,14,17,18,19,34] Nevertheless, a recent study from another centre in South Africa demonstrated a low early mortality rate of 13%,[16] which is comparable to findings at centres in Europe[17] and North America.[19] A slight male predominance was observed in our study, contrary to findings reported in several other institutional studies.[16,17,21,22,23]

Most patients received ATRA soon after morphological diagnosis. However, the under-utility of the initial peripheral blood smear at referring centres delayed the diagnosis and transfer to the treatment centre ($P = 0.01$). Equally concerning was that almost a fifth of patients did not have APL reported on the blood smear performed at index presentation, which might be a consequence of inexperienced technologists and the absence of an on-site pathologist at peripheral centres. Conversely, despite all patients from Lesotho having a morphological diagnosis of APL on index presentation, delays in transfer occurred in most cases. Suspicious peripheral smears identified by laboratory professionals in Lesotho are transferred across an international border to a private laboratory in South Africa, but these delays could not be measured. In most cases, initiation of treatment was not dependent on confirmatory diagnosis by FISH or PCR.

Baseline PCR for t(15;17) was not requested for most patients before induction therapy. The utility of qualitative PCR t(15;17) has become increasingly important, with several studies highlighting the prognostic implications between the variant *PML-RARA* breakpoints.[21,34,35] Additionally, quantitative PCR t(15;17) at baseline remains important in later assessments for minimal residual disease.[33]

A unique feature among the study population was the observation of hypogranular APL being the predominant type, which, to the researchers' knowledge, is the first time this has been reported in an institutional cohort.[16,17,18,19,28,30,31] Despite this finding, morphological variance alone was not significantly associated with either the 7-day or the 30-day mortality.

Bleeding complications were a prominent finding among patients. All patients met laboratory criteria for DIC, three-quarters of whom had supportive clinical features of DIC at presentation. Death because of bleeding and thrombotic complications occurred within the first seven days of presentation, while infection and differentiation syndrome accounted for deaths thereafter. This might be explained in part by a delay in diagnosis and transfer of patients, which was observed in two cases (*n* = 2/5; 40.0%) who died within the first week of presentation. Importantly, patients were classified as high risk and ultra-high risk by the Sanz and

TABLE 6a: Comparison between the demographic and laboratory parameters with the short-term (7- and 30-day) outcome of patients with acute promyelocytic leukaemia.

Variables	Outcome at day 7							Outcome at day 30						
	Deceased			Alive			*p*	Deceased			Alive			*p*
	n	Median	IQR	*n*	Median	IQR		*n*	Median	IQR	*n*	Median	IQR	
Patients	5	-	-	22	-	-	-	9	-	-	18	-	-	-
Demographic characteristics														
Age (years)	-	29	26–33	-	33.5	19–49	0.55	-	32	26–35	-	33	19–52	0.49
Gender	-	-	-	-	-	-	1.00	-	-	-	-	-	-	1.00
Male	3	-	-	12	-	-	-	5	-	-	10	-	-	-
Female	2	-	-	10	-	-	-	4	-	-	8	-	-	-
Baseline laboratory investigations														
FBC at presentation														
Haemoglobin	-	8.1	7.2–11.7	-	6.1	5.3–8.1	0.05	-	8.1	6.7–9.1	-	6.1	5.3–7.5	0.12
White cell count (× 10^9/L)	-	58.10	50.16–92.93	-	4.91	2.11–13.39	0.01	-	50.16	39.21–62.94	-	4.91	2.11–13.26	0.03
≥ 10	5	-	-	9	-	-	0.04	7	-	-	7	-	-	0.10
< 10	0	-	-	13	-	-	-	2	-	-	11	-	-	-
Neutrophil count (× 10^9/L)	-	1.46	0.99–9.29	-	0.22	0.08–0.88	0.01	-	1.46	0.99–3.14	-	0.22	0.08–0.67	0.06
Platelet count (× 10^9/L)	-	19	14–24	-	15	12–31	0.89	-	23	14–26	-	14	12–28	
≥ 40	1	-	-	7	-	-	1.00	0	-	-	2	-	-	0.54
< 40	4	-	-	15	-	-	-	9	-	-	16	-	-	-
Coagulation studies at presentation														
Prothrombin time (s)	-	17.5	16.7–19.5	-	15.9	15.3–16.6	0.06	-	17.5	16.2–20.3	-	15.9	15.3–16.5	0.73
Partial thromboplastin time (s)	-	27.4	24.8–30.7	-	25.1	22.5–29.7	0.22	-	27.4	25.3–32.9	-	24.3	22.2–30.5	0.02
Fibrinogen (g/L)	-	1.1	0.8–2.7	-	1.7	1.3–2.7	0.42	-	1.3	1.1–2.7	-	2.0	1.5–2.7	0.78
D-dimer (µg/mL)	-	17.6	15.3–19.0	-	15.3	8.2–24.0	0.60	-	15.3	8.2–19.0	-	16.7	8.9–24.0	0.59
DIC score	-	6	6–8	-	6	6–6	0.15	7	-	-	6	-		0.13
Creatinine (µmol/L)	-	164	77–294		75	64–85	0.13	-	77	70–164	-	76	64–86	0.74
≥ 105 µmol/L	3	-	-	0	-	-	0.003	3	-	-	0	-	-	0.03
< 105 µmol/L	2	-	-	22	-	-	-	6	-	-	18	-	-	-
APL morphological characteristics														
Type	-	-	-	-	-	-	0.48	-	-	-	-	-	-	0.20
Hypogranular	4	-	-	11	-	-	-	6	-	-	9	-	-	-
Hypergranular	1	-	-	10	-	-	-	2	-	-	9	-	-	-
Unknown	0	-	-	1	-	-	-	1	-	-	0	-	-	
Risk stratification														
Sanz score	-	-	-	-	-	-	0.04	-	-	-	-	-	-	0.15
Low	0	-	-	1	-	-	-	0	-	-	1	-	-	-
Intermediate	0	-	-	12	-	-	-	2	-	-	10	-	-	-
High	5	-	-	9	-	-	-	7	-	-	7	-	-	-
Modified Sanz score	-	-	-		-	-	0.03		-	-	-	-	-	0.12
Low	0	-	-	1	-	-		0	-	-	1	-	-	-
Intermediate	0	-	-	5	-	-	-	1	-	-	4	-	-	-
High	1	-	-	13	-	-	-	3	-	-	11	-	-	-
Ultra-high	4	-	-	3	-	-	-	5	-	-	2	-	-	-

APL, acute promyelocytic leukaemia; DIC, disseminated intravascular coagulation; FBC, full blood count; IQR, interquartile range.

TABLE 6b: Comparison between the demographic and laboratory parameters with the short-term (7- and 30-day) outcome of patients with acute promyelocytic leukaemia.

Cause of death	Died within first 7 days	Died within first 30 days
Bleeding	3	0
Ischemic CVA	2	0
Infection	0	4
Differentiation syndrome	0	1
Unknown	1	0
Total	**5**	**4**

CVA, cerebrovascular accident.

modified Sanz scores, both predictors of mortality, within the first seven days.

The marked occurrence of coagulopathy at presentation emphasises the need for adequate transfusion support during induction therapy. This is challenging in a resource-limited setting, both financially and regarding the availability of blood products. Despite similar numbers, patients in the Sanz high-risk group received significantly ($p = 0.01$) fewer red cell transfusions than the non-high-risk group – likely a consequence of the longer duration of hospitalisation in the latter group, none of whom died within the first week of presentation.

While the availability of ATO has increased globally, access to ATO as first-line therapy remains a significant challenge at UAH. This resulted in all patients being initiated on an anthracycline-based chemotherapy regimen, which was not the current international standard of care in the 12 non-high-risk patients.[33]

Although most patients were classified as high risk and ultra-high risk upon the first presentation, neither the Sanz nor the modified Sanz scores were significant predictors of

30-day mortality. This was contrasting to the 7-day mortality in which both risk groups were associated with death in the first seven days of presentation ($p = 0.04$ and $p = 0.03$, respectively). Additionally, a white cell count of $> 10 \times 10^9$/L was associated with 7-day mortality ($p = 0.03$). Patients who died within the first seven days of admission were found to have a significantly higher median white cell ($p = 0.01$) and neutrophil count ($p = 0.01$). Similar to previous studies, patients who died within the first 30 days of admission were found to have significantly higher median white cell counts ($p = 0.03$)[22,27,34] and partial thromboplastin times ($p = 0.02$).[34]

While the clinical haematology unit at UAH uses the Sanz classification for risk stratification, if these patients were to be risk stratified according to the updated recommendations from the European LeukemiaNet (ELN), they would fall into the high-risk patient category (WCC $> 10 \times 10^9$/L).[33] Considering the high mortality rate in patients with WCC $> 10 \times 10^9$/L and the recommendation to use ATO upfront in high-risk patients according to the ELN guidelines[33], 7-day mortality may be improved by the addition of ATO in this risk group. This finding may be useful to motivate the availability of ATO at UAH.

A creatinine level of ≥ 105 µmol/L was associated with both 7-day and 30-day mortalities ($p = 0.003$ and $p = 0.03$, respectively). Conflicting findings regarding elevated creatinine and early death have been reported. During the development of the modified Sanz score, Lou et al.[27] found no association between creatinine levels of ≥ 105 µmol/L and death before or during the first 30 days of induction among a cohort of 426 newly diagnosed APL patients. More recently, a single-centre study comprising 91 patients between 2 and 21 years of age demonstrated an association between creatinine levels of ≥ 0.7 mg/dL (61.9 µmol/L) and death within 30 days of diagnosis of APL.[36] These findings were similar to De la Serna et al.,[37] where a creatinine level of ≥ 1.4 mg/dL (123.8 µmol/L) was associated with death during induction. The proposed mechanism behind the elevated creatinine levels in both studies was microthrombi of the renal vasculature. Among the three patients with a creatinine level of ≥ 105 µmol/L in our study, the possibility of this proposed aetiology was supported by leukocytosis (white cell count range 41–92 $\times 10^9$/L), overt DIC at presentation and thrombosis at other organ sites. The Cairo–Bishop definition for tumour lysis syndrome[38] was not met in any of the patients.

Study limitations

Although this study represents all adult patients treated at UAH, the small sample size may limit generalisability of findings. The availability of ATRA outside the tertiary setting is challenging in an upper-middle-income country, and data regarding pre-referral patient management (including transfusion of blood products and ATRA administration) were unknown. The consequence of this situation was of particular concern for patients who died within the first week of presentation.

This study aimed to provide insight into the short-term outcome of APL without considering long-term mortality at UAH, which is still unknown. A selection bias is acknowledged, as only patients who were referred and alive at the time of arrival were included in the study. This bias is important, considering high-risk patients and the 7-day mortality.

Recommendations

The most crucial obstacle to treatment initiation currently remains early recognition and referral to a specialist centre. Cost-saving measures at peripheral healthcare facilities often limit extensive investigations. However, given the high mortality of APL at UAH, combined with the significant impact on resources such as blood products, intensive care facilities and the prolonged hospital stay that patients experience, we recommend that every patient with an abnormal FBC, especially with cytopenia or leukocytosis, have an accompanying peripheral blood smear performed.

The lack of pathologists outside the tertiary setting in our country necessitates education and outreach programmes to peripheral centres that may contribute to the prompt diagnosis of APL. It is pivotal to avoid treatment delays while awaiting the transfer of high-risk patients. Blood products and ATRA need to be available and accessible at both regional and district levels. At a tertiary level, quantitative PCR remains underutilised, and it is recommended at baseline and for treatment monitoring purposes.

Potential future studies to determine the long-term survival of patients with APL and a larger study cohort may add to the pool of knowledge on this rare condition.

Conclusion

Globally, this is the first study that shows a predominance of the hypogranular type of APL, although it was not associated with short-term mortality. Despite the high 30-day mortality, the Sanz and modified Sanz scores were not predictors of outcome at 30 days in this study but were instead associated with 7-day mortality. A creatinine level of ≥ 105 µmol/L was found to predict both 7-day and 30-day mortalities, while a WCC of $> 10 \times 10^9$/L was a predictor of 7-day mortality. Patients who died within the first seven days had a significantly higher median neutrophil and WCC, whereas those who died within the first 30 days had a significantly higher median WCC and partial thromboplastin time. The short-term mortality of APL at UAH was more in keeping with findings at other treatment centres in upper-middle-income countries, with factors such as transport inadequacies, availability of treatment and limited staff and resources being additional impediments in the management of APL.

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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

The research question and study design were formulated by W.N., C.B. and J.K. The protocol was written by W.N. and supervised by C.B. and J.K. Data collection was done by W.N. Confirmation of morphological types was performed by A.v.M. The manuscript was written by W.N. and supervised by C.B. and J.K. The final work was edited by C.B., J.K. and A.v.M. C.v.R. assisted with the study design and performed the statistical analysis. All the authors approved the final version of the article.

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Data availability

All data collected in this study are available from the corresponding author, W.N., upon reasonable request.

Disclaimer

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