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# *Geographic Diversity and Management of CLL in African Patients*

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# Disclosures

- None

# Learning Objectives

1) To assess the different presentations of chronic lymphocytic leukaemia (CLL) in Africans in relation to
    1) prevalence
    2) geographical location,
    3) age at diagnosis,
    4) sex distribution,
    5) clinical features,
    6) staging systems, and
    7) laboratory investigations.
2) To evaluate the different outcomes of the treatment of CLL in Africans in relation to
    1) treatment environment,
    2) protocol/regimen,
    3) survival (OS),
    4) complications, and
    5) prognostic indicators.

# Introduction

- Chronic lymphocytic leukaemia (CLL) is a complex disease with variable presentation and response to therapy.
- Although CLL is the most common type of leukaemia in Western populations, it is rare in Africans.
- For this review, a literature matrix of the abstracts and full texts related to CLL in Africans was made.


**Figure 1: 58 African Countries**

# African Population by Country (Top 9), 2017

Nigeria (193m; 15.38%)
Ethiopia (99.4m; 8.37%)
Egypt (97m; 7.65%)
Democratic Republic of the Congo (86m; 6.57%)
South Africa (55m; 4.55%)
Tanzania (51m; 4.47%)
Kenya (3.88%)
Sudan (3.38%)
Algeria (3.36%)
Other (42.39%)

**TOTAL POPULATION 1.25b**

Wikipaedia

# Literature Review

- Fourteen abstracts/full texts from African countries (1984 to 2017) were included in this review:
  - Senegal,
  - Ivory Coast,
  - Nigeria (7),
  - Cameroon (a case report),
  - Kenya (comparative),
  - Algeria (comparative),
  - Uganda/UK (comparative; CLL-phenotype MBL); and
  - Zimbabwe.
- Five comparative articles from America (2011 to 2016).
- There were missing data in every article reviewed.

# Table 1: Literature Matrix

| Considerations | Williams CK., Some biological and epidemiological characteristics of human leukaemia in Africans | Fleming CLL in Tropical Africa | Okpala and Okpala, Socio-economic class distribution of the prognostic variants of lymphoproliferative cancers in Nigerians | Mukiibi et al CLL in Central Africans | Omoti and Imiere Pattern of Leukaemia Incidence in a Tertiary Institution | Omoti et al., Chronic lymphoid leukaemia: clinico-haematological correlation and outcome in a single institution in Niger Delta region of Nigeria | Koffi et al., Chronic lymphocytic leukemia in Subsaharian Africa: clinical outcome experience of Côte d'Ivoire | Salawu et al - a 20-yr Review at OAUTHC,Ile-Ife, Nigeria 1990-2009 | Shenoy et al., Racial Differences in the Presentation and Outcomes of Chronic lymphocytic Leukemia and Variants in the United States | Omoti et al., Epidemiological features of Lymphoid malignances in Benin City, Nigeria a 15 year Review | Coombs et al., Single nucleotide polymorphisms and inherited risk of chronic lymphocytic leukemia among African Americans | Falchi et al., Clinical Characteristics, Response to Therapy, and Survival of African American Patients Diagnosed With ChronicLymphocytic Leukemia | Mulwa-Babu et al., Chronic lymphocytic leukemia in Kenya: an immunophenotypic and clinicopathologic study | Dali et al Review of Epidemiology of CLL by the Algerian CLL Study Group | Alkatib et al., Racial Impact and Cytogenetic variations and Outcome of CLL | Sall et al. Characteristics of CLL in Senegal | Nabhan et al., Analysis of racial variations in disease characteristics, treatment patterns, and outcomes of patients with chronic lymphocytic leukemia -20yr review (1995-2014) | Rawstron et al., Monoclonal B-cell lymphocytosis in a hospital-based UK population and a rural Ugandan population: a cross-sectional study | Founou et al., A case report of CLL in a Black African man. (Cameroon) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Journal | IARC Scientific Publications 1984(63): 687-712 | Leukaemia and Lymphoma vol 1: 169-173 | Afr. J. Med. Med Sc Vol 1:79-83 | KAJM vol. 50, | J. Medicine and Biomedical Research Vol 5: 44-49 | Int. J. Lab. Hematol 29: 426-432 | Bull Cancer 96:901-906 | African Health Sciences Vol 10: 187-192 | Clinical Lymphoma Myeloma and Leukaemia Vol 11:498-506 | The Pan African Medical Journal. 2012;11:10 | Blood 120:1687-1690 | Cancer 119: 3177-3185 | J. Afr. Cancer vol 5: 192-197 | Blood 126: 5274 | Blood 128: 3209 | BMC Hematol 16:10 | Am J Hematol 91: 677-680 | Cancer | Journal of Leukaemia |
| | full text | abstract | abstract | abstract | full text | abstract | full text | full text | abstract | full text | full text | full text | full text | abstract | abstract | full text | full text | full text | full text |
| Year of publication | 1984 | 1990 | 1992 | 2004 | 2006 | 2007 | 2009 | 2010 | 2011 | 2012 | 2012 | 2013 | 2013 | 2015 | 2016 | 2016 | 2016 | 2017 | 2019 |
| country | Ibadan, Nigeria | West and South Africa | Ibadan, Nigeria | Zimbabwe | Benin, Nigeria | Benin, Nigeria | Abijan, Ivory Coast | Ile-Ife, Nigeria | America | Benin, Nigeria | America | America | Kenya | Algeria | America | Senegal | America (Mayo Clinic) | UK and Uganda | Cameroon |
| number of patients | 31/146 | | 120 lymphoproliferative cases | | 54/253 | 65 | 56 | 78 | 30,622 (CLL/SLL) | 197/1081 (1996-2010) | 112; 42; 68 | 94/1571 | 42/49 B/NB | 1210 | 177 (112 : 65 Blacks) | 40 | 101 vs 4114 | 302 | 1 |
| prevalence/incidence | 21.2% of leukaemias | | | | 21.30% | 26.4% of leukaemias | | 88.1% of chronic lymphoid leukaemias | | 18.20% | | | | 0.66/100,000 | | | 1% vs 7% | | |
| Age (median/range | | >45 and >45 years | | >50yr | | 56 (51-60) | 62 (38 - 84) | 60 (30 - 81) | 67 vs 71 | 59yr males 56 females | | 59 (35-88); 59 (26-94) | 62 (45-95) females younger 20yr younger st | 67.5 (33 - 98) | | 61 (48-85) | 59.4 vs 63.4yr | 40-60 >60yr | 54 |
| M: F ratio | 1.6 <50 and 5.3:1 >50yrs | 1:1 1-2 | | | 02:01.2 | 01:04.4 | 01:01 | 0.8:1 | 1.89 (overall) | 01:01.2 | | 1.3:1; 1.55:1 | 1.3: 1 | 2.2: 1 | | 1.44: 1 | 2.5: 1 vs 2: 1 | 121: 47 and 90:44 | male |
| clinical features at diagnosis | | massive splenomegaly; 2 populations of lymphocytes in PBF. | | peripheral LN -90-95% | | LN enlargement 91.7%; anaemia 58.3%; splenomegaly 50% | massive splenomegaly, LN, WBC >100,000, anaemia and thrombocytopenia | massive splenomegaly 70.9%; hepatomegaly 29.1% ; anaemia 74.7%; WBC >30,000 - 70%; platelets <90,000 - 48.6% | Blacks had more extra nodal site involvement; B symptoms; advance disease than Whites | | | AA were more anaemic, higher b2-microglobulin, more constitution symptoms | Lymphadenopathy 29/49 (59.2%); Splenomegaly 25/49 (51.0%); Hepatomegaly 8/49 (16.3%) Presence of any B symptom 14/49 (28.6%) | tumoral syndrome; WBC - 92.5 x $10^3$; (5.0-900) | | | LDH higher in NW than Whites | monoclonal B-cell lymphocytosis (MBL) | generalised LN; PBF - lymphocytosis; pain; fever; cough. |
| stage of disease | | | | | | Binet B and C 88.3% | 27/56 Binet B and C | Binet C >63% | | | | more in Rai 3/4 | Rai 3/4 Hb < 11g/dL - 18/49 (36.7%); platelets <100 x $10^9$/l -9/49 (18.4%) Binet B/C (53.1%) | Binet C 41.1% | Rai 2 majority | Binet B and C 82.5% | same | Binet A | B |
| diagnosis (morphology) % | | 100%? | | | | 100% | | 100 | | | | | yes 100% | 88.20% | | | yes | | |
| Flow-cytometry - immunophenotype | | | | | | | | N/A | | | | | yes CD5 and CD 23 in 95.9% | 61.60% | 13q14 | CD38+ | similar | CD19, CD20, CD27, CXCR5, and LAIR1; CD38, CD73, CD200, and CD307d (FcRL4) | CD5+, CD19+, CD23+, CD20+, CD43+, CD79b-, FMC7-, and the surface lamba light chain (weak intensity) |
| cytogenetics | | | | | | | | N/A | | | | more unmutations in IGHV; 2AP70 expression is more; more deletion abnormalities | | 8.40% | | 68% had one abnormality and 28% had two | similar for 13q, tri 12, 11q and 17p | productive, in-frame IGHV-IGHD-IGHJ gene rearrangements sequenced per individual | |
| Screening for infection - HIV, HBV, HCV | | | | | | | | yes | | | | | | | | | | yes HIV | yes/all negative |
| Time to First Treatment | | | | | | | | 27.80% | | | | 14.3m and 57.2m | | | | same | | | 7 years |
| treament modality | | | | | | | CVP, Chlorambucil, CHOP | chlorambucil, CVP | | | | CR and similar no. of cycles | | | | same | similar | | chloramiophene |
| no treatment | | | | | | | | | | | | | | | | | | | |
| complications | | | | | | | | | | Richter's disease 5% | | | | | | | | | |
| survival/outcome | | | | | | 2yr 27.2% and 28.9% for <35yrs and >50yr respectively | | 8.2yr; 5yr survival 58.8% | 70.2% at 2 years | 5-yr 63.9 vs 77.1% | | | median survival was shorter for AA 152m vs unreached | | | | no difference | no difference | similar | |
| Position among haemato-oncology conditions | | | | | | | | | | | | | | 5th | | | | | |
| Risk factors | lower SES than CML patients | low SES; overcrowding; immune suppression by malaria; pregnancy. | low SES | | | | | low SES | | unemployment and oil producing States | SNPs not significantly different (?? Small numbers) | | | farming | no difference between Caucasians and African Americans | | | CD38, CD73, CD200, and CD307d (FcRL4) 5 times more in MBL than polyclonal patients. SNPs associated with CLL-phenotype low. | nil observed |
| Conclusion | The epidemiological features of ALL and CLL in Africans suggest a role for the influence of life-style in leukaemogenesis while the clinical patterns of these disorders suggest that the biological characteristics differ from those of similar diseases in developed countries. | HTLV-1 is associated with CLL, but does not appear to contribute significantly to the peculiar epidemiology of CLL in Africa | The precise mechanisms by which socio-economic strata influence development of the different prognostic variants of individual lymphoproliferative cancers are not certain | suggested that differences may be due to genetic determinants. | Chronic leukaemias more prevalent than acute and genetic studies are needed to determine the preponderance of CLL in females in the African setting. | Studies on the genetic make up/HLA typing of patients of African descent are needed to clarify some of the differences observed | Age, adenopathy, hepatomegaly and lymhocytosis were independent prognostic factors for predicting survival. | Massive splenomegaly is a common finding in the majority of patients. Non-availability of immunophenotyping is a major constraint | Epidemiological studies examining the biological variants of three diseases in concert with race are needed to elucidate the etiology of these disparities. | increasing number of cases and male excess in lymphoid malignancies (except CLL) requires further study regarding lymphomagenesis including research into environmental agents | A fuller understanding of differential genetic risk using GWA may improve prognostication and therapeutic decision making for all CLL patients | AA patients with CLL have more unfavorable prognostic characteristics and shorter survival compared with their NB counterparts. | Black had more lymphocytes than NB who presented earlier. Immunophenotyping is diagnostically productive and should be part of the diagnostic workup when a chronic lymphoproliferative disorder is suspected. | The incidence is still low in Algeria; it affects elderly people with a masculine predominance as in the other countries. | Racial difference should not be taken into account when treating patients with newly diagnosed CLL, since there is no evidence that outcomes are different when treated with conventional therapy | Africans may present with CLL at a younger age and our data suggest that CLL in Senegal may be more aggressive than in Western populations | These findings suggest previously noted outcome differences may be due to disparities in access to care and management rather than differences in disease biology. | Although MBL is common in both rural Uganda and the UK, the variation in phenotype shows that differences in environmental exposure, inherited susceptibility, or both factors affect the type of B-cell neoplasms that can develop. | This case demonstrates the importance for the physicians to be aware of the increasing existence of CLL among patients of various ages and without risk factors. |

KEY:
YELLOW - the year of publication;
GREEN - African country;
RED - Missing data;
BLUE - similarity.

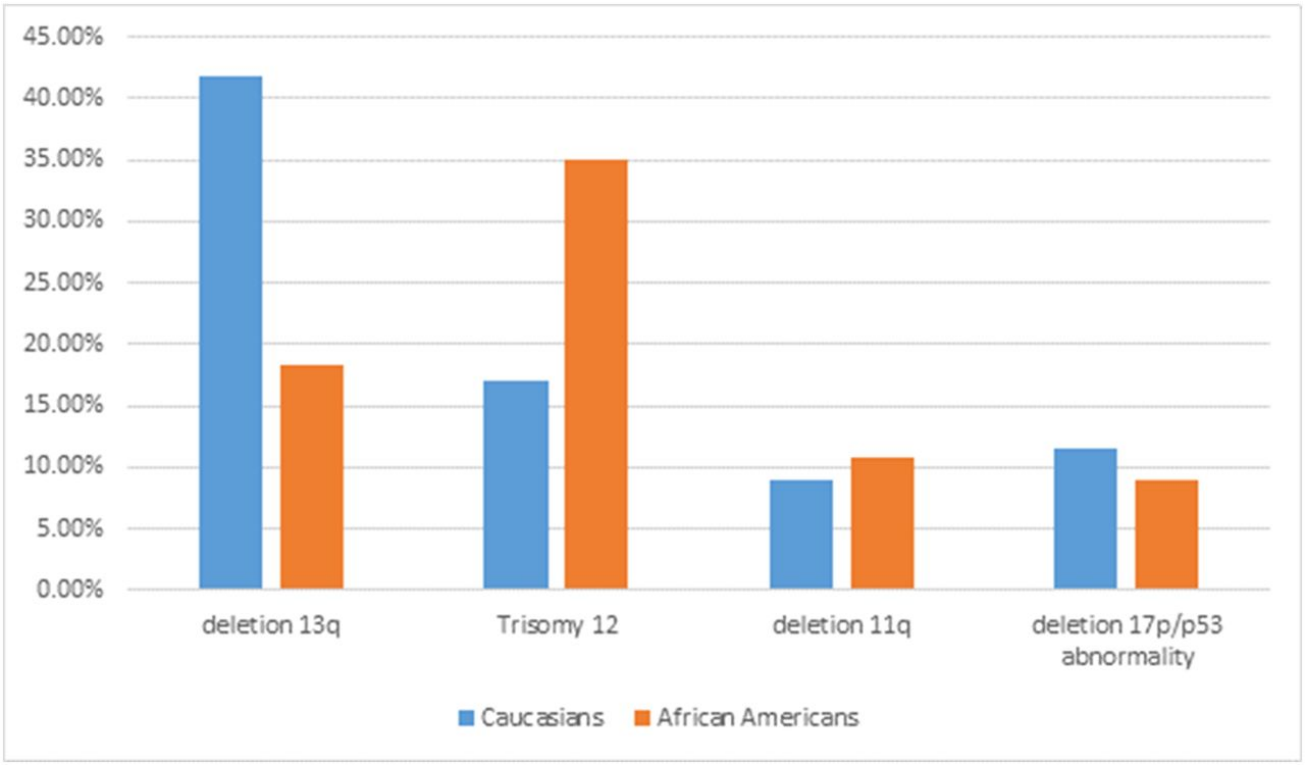
# Table 2: Clinical Features at Presentation

| Features | Africans | Non-Africans |
|---|---|---|
| Number of patients | 1 – 1210 (Dali et al., 2015) | 68 – 4114 (Nabhan et al., 2016) |
| Prevalence/Incidence | < 0.66/100,000 (Dali et al., 2015) | <1 – 5.5/100,000 (WHO) |
| Median Age (yrs) at diagnosis (range) | 56 – 67 (29-98) | 59 – 71 (26-94) |
| Male: Female ratio | 0.8: 6 – 3.44: 1 (variable) | Male preponderance (1.8 - 2.5: 1) |
| Clinical features | ↑ LN, Splenomegaly, Anaemia, more B symptoms | Fewer LN, splenomegaly, fewer B symptoms |
| Stage at diagnosis | Binet B and C; Rai 2 to 4 | Binet A and B; Rai 2 |

# Laboratory Investigations

- Africans have been found to have
  - Higher lymphocyte counts in the peripheral blood (Dali et al., 2015);
  - lower median haemoglobin levels;
  - higher beta$_2$-microglobulin ($\beta_2$-m) levels;
  - Higher LDH; (Nabhan et al., 2016)
  - unmutated IGHV gene (65% versus 47%);
  - ZAP70 expression (58% versus 32%); and
  - chromosome 17p or 11q deletion (28% versus 17%), (Falchi et al., 2013)
  - similar for 13q14, tri 12, 11q and 17p (Nabhan et al., 2016)
  - Immunophenotyping characteristics CD5, CD23, FMC7, CD22 are similar (Nabhan et al., 2016)
  - Screening for common viral infections HIV, HBV, HCV were negative in majority of patients. (Salawu et al., 2010; Rawstron et al., 2017)

# Figure 2: Cytogenetic Abnormalities in CLL




**Yaser Alkhatib et al. Blood 2016;128:3209**

# *Management of CLL in African Patients*

# Treatment Modalities

- Watchful waiting (28.7%; Salawu et al., 2010)
- Chlorambucil
- CVP
- CHOP
- Fludarabine (expensive)
- FCR (similar response; Falchi et al., 2013) (expensive)
- Ibrutinib X not available

# Outcomes of Treatment

- Some studies found no difference in the outcome and OS between African and non-African patients (Alkabit et al., 2016; Sall et al., 2016; Nabhan et al., 2016)
- A study showed that African American patients had a markedly shorter median time to first therapy (14.3 months versus 57.2 months) than non-African patients. (Falchi et al., 2013) However, a study from Senegal (Sall et al., 2016) reported no difference.
- African American patients had a significantly shorter median event-free survival (36 months versus 61 months; P = 0.007) despite having similar overall response rates. (Shenoy et al., 2011; Falchi et al., 2013)
- 2-year survival for African patients was variable at 27.2% and 75% Omoti et al., 2007and Salawu et al., 2010 respectively.
- 5-yr survival was 63.9 vs 77.1% for African and non-African patients respectively. (Shenoy et al., 2011)
- Overall survival (152 months versus not reached, P = 0.0001) (Falchi et al., 2013)

# Risk Factors

- Largely unknown. Many patients do not have any noticeable factor and very few have a family history.
- A report observed similarity between Africans and non-Africans. (Alkatib et al., 2016)
- The following factors have been suggested:
  - Social economic strata (SES) (Williams 1984; Fleming 1990 ; Okpala and Okpala 1992; Salawu et al., 2010; Omoti et al., 2012)
  - Malaria (Fleming, 1990)
  - Pregnancy (Fleming, 1990)
  - Farming (Dali et al., 2015)
  - Immune suppression (Fleming, 1990)
  - Exposure to petro-chemicals (Omoti et al., 2012)
- SNPs have been studied with diverse results of racial differences found. (Coombs et al., 2012; Rawstron et al., 2017)

# Can Animals have CLL?

# Can animals have CLL?

- Yes.
- Haematologic malignancies has been reported in domestic animals, (Gabor et al. 1998; Harrison et al. 2010) but reports of non-domestic animals are rare.
- A case report of a 15-year old female African lion (*Panthera leo*) in the Zoological Gardens of Pistoia, Tuscany, Italy. (Meoli et al., 2018).
- The lion presented with malaise, dyspnoea, tremors and pale mucous membranes.
- She had ataxia for two days prior to death.
- CBC showed anaemia, thrombocytopaenia and severe lymphocytosis.

# The African Lion with CLL

- At autopsy, the most significant observation was massive splenomegaly.
- Histologically, the spleen, liver, heart, pancreas, kidney and lungs were diffusely infiltrated by malignant lymphocytes, which were positive for CD79a and negative for CD3 on immunohistochemistry.
- These features are consistent with B-cell lymphocytes and a diagnosis of CLL was made.

Figure 3: A free Internet Photo

# Summary

1) At presentation, Africans with CLL
    a. have a lower prevalence/incidence than non-Africans;
    b. have diverse presentations no matter their geographical location;
    c. have a more aggressive disease;
    d. Male to female ratio is variable, but they are more likely to be female especially below the age of 55 years;
    e. Present late (Binet B and C stages);
    f. have higher LDH levels; and
    g. have variable cytogenetic and molecular abnormalities.
2) Outcomes of the treatment of CLL in Africans
    a. Despite similar treatment conditions as non-Africans, African patients respond poorly;
    b. survival of Africans is less than 75% at two years;
    c. ZAP70, a marker of poor prognosis, occurs more frequently in African patients; and
    d. CLL in Africans may transform in about 5% of cases.

# Transformation??: African in Dressing, but Genetically non-African

These are non-African students are learning Yoruba language at the University of Wisconsin, USA.

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# Thank you for your attention.