

Prevalence of Anaemia and Pulmonary Mycoses in Immunocompromised Subjects: A Review of Nigeria Perspective

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1.Operational definition; that could help to understand some term according to your review. Example immune-compromised, etc?
2.Abbreviation and/ or acronyms

ABSTRACT

Anaemia and mycoses are being diagnosed with increasing frequency among immuno-compromised subjects. Fungal respiratory infections are important causes of mortality and morbidity among immuno-compromised individuals. The goal of this research was to systematically review the prevalence of anaemia and mycoses among immuno-compromised subjects in Nigeria based on published articles. We reviewed a total of 23 studies published between 2009 and 2021 comprising retrospective studies, cross-sectional studies and case reports. The overall prevalence of anaemia in this study was between 16.2%-75.5% while mycoses prevalence was between 8.7-73.6% among immuno-compromised subjects in reviewed Nigerian populations. This study revealed that the prevalence of anaemia in South-South, South-East and Abuja (North Central Nigeria) were between 47.4%-73.5%, 44.6%-75.5% and 16.2% respectively among immuno-compromised HIV/AIDS and/or TB co-infections. The prevalence of mycoses in South-South, South-East, Western Nigeria and Northern Nigeria were between 25.3%-36%, 22.4%-52.5%, 8.7-33% and 12.7%-73.6% respectively among immuno-compromised subjects. This study confirm that anaemia and mycoses are common among immuno-compromised subjects in Nigeria; with pulmonary tuberculosis and low CD4 being important risk factors.

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Keywords: Prevalence; Immunocompromised subject; Anaemia; Mycoses; Opportunistic infections.

1. INTRODUCTION

People with immuno-compromised system are vulnerable to secondary infections and malignancies that are generally termed as opportunistic infections [1,2]. Individuals susceptible to pulmonary mycoses include those with immuno-suppressive illnesses like HIV/AIDS [1-5], diabetes [6-8], tuberculosis [3,9,10], cancer [7], chronic pulmonary diseases(COPD), immune-modulator therapy for the prevention of rejection in solid organ and hemaetopoietic cell transplantation [7,11,12]. Fungal infections of the lung are among the most feared infections in immuno-compromised patients. Fungi like *Aspergillus* species, *Candida* species, *Cryptococcus* species are common ubiquitary opportunistic pathogens affecting the lung, especially in immuno-compromised people [1-5,7,9,10,13]. The *Aspergillus* species forms a genus of

ubiquitous, dimorphic molds present in soil, air, various types of organic debris, water, indoor environment and many other sites; forming commonest pathogens responsible for mycoses in immuno-suppressive individuals [1-4,7,9-13]. *Aspergillus* species caused pulmonary aspergillosis; especially in immuno-compromised subjects [14-16]. HIV is a multi-systemic infection that suppresses haematopoietic system [13,17]. HIV/AIDS is a global pandemic disease [1-3,18] contributing to health burden in developing countries [1-3]. Diabetes mellitus continues to be a global health problem with over 80% of affected people living in low-middle income countries (LMICs) where tuberculosis is widespread [2,6-8]. Nigeria is ranked fifth among the 22 nations with high tuberculosis burden [2, 6] with new and relapsed cases of tuberculosis occurring [7,8]. Anaemia is a major public health problem, especially in developing countries [18-20]. It is the most important clinical problem observed in people living with HIV/AIDS [18-20] and other immuno-compromised subjects; its severity increases as CD4 count declines [2-3,19,20] and with progression of HIV to advanced stage [18]. Additionally, the higher anaemia level is also a good opportunity for HIV/AIDS progression irrespective of CD4 counts level and viral load [18-21]. Moreover, anaemia influences the natural history of HIV/AIDS [18,21], resulting in the decrease of the survival rate [19-22]. HIV/AIDS and anaemic condition have significant consequences on health, social and economic development of individuals [18]. The most common causes of anaemia are chronic infections like TB, HIV/AIDS [3-5,18-20], deficiency of mineral, iron, and vitamin B12 [23] and genetic defects [24]. Prevalence of pulmonary mycoses and anaemic conditions among immuno-compromised subjects in Nigeria and other African countries are on the increased [1-5, 9-11]; resulting to public health burden in the region. Therefore periodic review of published articles on the prevalence of mycoses and anaemic conditions among

immuno-compromised subjects in Nigeria is imperative to ascertain the prevalence in the region. This information will be useful for prompt actions to be taken by health practitioners. This study seek to review relevant published researches on prevalence of pulmonary mycoses and anaemia among immuno-compromised subjects in Nigeria from 2009 to 2021.

2. MATERIALS AND METHODS

2.1. Study Design and Searching Strategy

Systematic review of relevant published articles in Nigerian populations were searched in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis [25]. All databases were searched from 2009 to 2021. Electronic databases search like Google Scholar, PubMed, EMBASE, MEDLINE, CAB HEALTH and Cochrane Library were performed. The search engine used detailed medical subject heading (MeSH), keywords/abbreviations such as: incidence/prevalence of opportunistic pulmonary mycoses (caused by *Candida* species, *Aspergillus* species, *Cryptococcus* species) among immuno-compromised subjects in Nigeria. The immuno-compromised subject included HIV/AIDS, diabetic patients and tuberculosis. Also, TB, Anaemia, heamatological parameters, hemoglobin, Hgb, Hb, the names of each states in Nigeria and her geopolitical regions were used for literature search.

2.2. Selection Criteria

Publications on retrospective study, cross sectional study, case study and case-control study conducted using primary data from Nigeria were selected for this study. From those studies meeting eligibility criteria, the first author's name, publication year, study area, sample size, study design and effect measure of anemia for immuno-compromised subjects were extracted. Only literature published in English Language

was used for this study. Review articles and cases with grossly missing data were excluded.

2.3. Brief Description of Study Area

Nigeria is one of the most densely populated countries in Africa, with approximately 200 million people in an area of 920,000 km²(360,000 square miles). She is one of the countries with the largest population in Africa and the seventh largest population in the world. Nigeria is situated in the West Africa region and borders Benin, Chad, Cameroon, and Niger. She has 36 states and the Federal Capital Territory (FCT) of Nigeria with diverse ethnic groups within six geopolitical zones as shown on Figure 1 [26,27].

2.4. Data Extraction

The online data extraction was performed independently by authors and any discrepancies were solved via discussions. Data on study authors, study location (country, region in Nigeria), study period, sex and clinical presentation or risk factors were equally extracted.

2.5. Statistical Analysis

Data analysis was performed using Microsoft Excel 365 and using Statistical Package for Social Sciences (SPSS) version 20.0. Categorical characteristics of studies (example: study design, state/region, cases, highlight of results) were summarized. Individual cases of pulmonary mycoses were summed up to give an overall number of patients diagnosed with pulmonary mycoses in Nigeria used for the study. Pulmonary mycoses among immuno-compromised subjects were stratified by state and region.



Figure 1: Map of Nigeria showing the different regions [26].

3. RESULTS

We retrieved 273 full texted publications initially from the database search and 30 identified from references of eligible studies. We then removed duplicates and 201 citations remained from which relevant studies were selected for review. Their potential relevance was examined using a title and abstract screening to remove studies that were clearly not related to scope of this review. A total of 280 publications were excluded and 23 were used for this review based on primary data on prevalence of anaemia and/or mycoses in immuno-compromised subjects (HIV/AIDS, TB and diabetic cases) in Nigerian populations between 2009-2021 (Figure 2). The overall prevalence of anaemia in this review study was between 16.2%-75.5% while mycoses prevalence was between 8.7-73.6% among immuno-compromised subjects in Nigerian populations. This study revealed that the prevalence of anaemia in South-

South, South-East and Abuja (North Central Nigeria) were between 47.4%-73.5%, 44.6%-75.5% and 16.2% respectively among immuno-compromised HIV/AIDS and/or TB co-infections. The prevalence of mycoses in South-South, South-East, Western Nigeria and Northern Nigeria were between 25.3%-36%, 22.4%-52.5%, 8.7-33% and 12.7%-73.6% respectively among immuno-compromised (Table 1).

Comment [u3]: How did you define immune-compromised? HIV/AIDS only or co-infection too?

4. DISCUSSION

This study recorded a prevalence of 8.7%-73.6% among immuno-compromised subjects. The prevalence of 55.6% was reported in Sao Paulo, Brazil among AIDS patients [44], 55.5% in Kano, Nigeria among HIV and TB co-infected subjects [30], 78.6% in Gombe, Nigeria among TB patients [29], 70.7% in Mbarara, South-Western Uganda [45], 12.8% in Beijing, China by Shailaja *et al.* [46], 47.6% in South African [47]. The differences in the prevalence of pulmonary mycoses in various populations may be attributed to the differences in sample size of recruited subjects,

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Figure2: Literature selection flowchart.

Table 1: Prevalence of anaemia and mycoses in Nigeria among immunocompromised subjects reviewed

Study design	City/year	State/Region	subjects	Cases	Result highlight(s)	Reference
Retrospective study	Calabar, 2013	Cross State/ South-South	HIV patients	272	-31.6% pulmonary mycoses and patients with mycoses were relatively younger. -overall prevalence for anaemia was 47.4%. - 18.4% were anaemic for mycoses positive subjects - Mild, moderate and severe anaemia was 36.4%, 12.7% and 9.5% respectively in females. Leucopenia, neutropenia, lymphopenia, thrombocytopenia and CD4 <300 was 15.1%, 9.3%, 45.3%, 1.2% and 94.2% respectively for mycoses positive cases.	19
Retrospective study	Calabar, 2013	Cross State/ South-South	HIV patients with some TB co-infections	272 HIV cases with 47 TB	-Overall prevalence of mycoses was 36% and mixed mycoses/TB was 7.7%. -The commonest fungi was <i>Candida</i> species (32.7%), followed by <i>Aspergillus</i> species. The commonest clinical conditions were cough (86%), chest pain (25.5%)	27
Cross-sectional study	Owerri, 2013	Imo State/ South-East	HIV subjects	339	-Overall prevalence of opportunistic infection (OIs) was 22.4% with more females having it. Candidiasis, cryptococcal meningitis and tuberculosis was 8.6%, 0.6% and 7.7% respectively. Baseline Hb <10 g/dl and CD4<200 for OIs was 46.1% and 50.7% respectively.	28
Retrospective study	Maiduguri, 2017	Borno State/ North-East	HIV/AIDS	150	-68% pulmonary mycoses with 69.3% and 66.1% for male and female respectively. The <i>Candida</i> species was more prevalent (38%), followed by <i>Aspergillus</i> species (18.6%). -HIV/TB coinfection was 90.2%.	2
Cross-sectional study	Gomba, 2020	Gomba State/ North-East	TB	216	-73.6% pulmonary mycoses with 69.5% and 36.5% for male and female respectively. -The <i>Aspergillus</i> species was more prevalent (61.1%), followed by <i>Candida</i> species (32%). -Prevalence was highest (27.7%) in younger age (30-38 years).	29

Table 1 Continued

Study design	City/year	State/Region	subjects	Cases	Result highlight(s)	Reference
Retrospective study	Kano, 2014	Kano State/ North-East	TB	200	-55.5% pulmonary mycoses ,63.06% were males and 36.94% were females. - Fungal species was highest in <i>Aspergillus</i> species (36.94%), followed by <i>Candida</i> spp. (36.04%)	30
Retrospective study	Abeokuta, 2016	Ogun State/ South-West	HIV/TB patients	272	-Male prevalence of pulmonary mycoses was 33% and female prevalence was 66.7%.	28
Retrospective study	Port Hacourt, 2020	Rivers States/ South-South	TB subjects	400	-The overall TB <i>Candida</i> co-infections was 34.4%. -The prevalence of TB among females was 22.4% and males 24.4% -High prevalence of <i>Candida</i> (25.0%) were between 31 - 40 yrs	31
Case study	Port Hacourt, 2016	Rivers States/ South-South	Diabetes mellitus	1	Chronic pulmonary aspergillosis and pulmonary tuberculosis	8
Cross-sectional study	Enugu, 2018	Enugu State/ South-East	Diabetic patients	120	-52.5% mycoses prevalence, <i>Candida</i> species was 20.8% while <i>Aspergillus</i> species accounted for 18.3%. -Co-morbid factors were HIV/AIDS, HBP and liver diseases with 1.7%, 30.8% and 0.8% respectively.	6
Retrospective study	Orlu, 2014	Imo State/ South-East	HIV patients	921	- 75.5% were anaemic for HIV positive subjects. -11.5% prevalence for HIV positive	32
Cross-sectional study	Enugu, 2020	Enugu State/ South-East	TB	303	-Prevalence of <i>Aspergillus</i> species causing pulmonary aspergillosis was 42.6% and other fungi was 13%. - <i>Aspergillus fumigatus</i> ranked highest (36.1%), others were <i>A.niger</i> (28.4%), <i>A. flavus</i> and <i>A. nidulans</i> (3.6%), <i>A.oryzae</i> and <i>A terreus</i> (2.4%) -High prevalence of pulmonary mycoses (37.3%) were between 31 - 40 years.	33

Table 1 Continued

Study design	City/year	State/Region	subjects	Case(s)	Result highlight(s)	Reference
Cross-sectional study	Kebbi, 2009	Kebbi State/ North	HIV subjects	606	-Prevalence of 61.7% for OIs. -Prevalence of tuberculosis (TB) was 6.7% while candidiasis was 8.6%. HIV prevalence was 31.6%.	34
Case study	Lagos, 2018	Lagos State/ South-West	TB subjects	1	-Chronic pulmonary aspergillosis	35
Retrospective study	Lagos, 2020	Lagos State/ South-West	HIV/AIDS	7034	-Opportunistic fungal infection was 18.6% and 21% had pulmonary TB. -Oral candidiasis was 0.3%, oesophageal candidiasis (8%), superficial mycoses (1.6%), Pneumocystis pneumonia (0.8%) and cryptococcal meningitis (0.4%). -The mean CD4 count was 184 cells/ μ l. HIV-1 viral load was 51,194 RNA copies/ml and 88% had initiated ART. Cohort death was 1.6%.	36
Cross-sectional study	Lagos, 2017	Lagos State/ South-West	HIV	156	-Chronic pulmonary aspergillosis (CPA) prevalence was 8.7%; 6.5% had HIV infection and 14.5% were HIV-negatives. -Mean CD4 count was 169.5 cells/ml (range 4–593) in HIV-infected patients with positive <i>Aspergillus</i> IgG. Overall, 52.4% had documented TB, 67.3% had a productive cough and 50 had haemoptysis.	37
Cross-sectional study	Maiduguri, 2018	Borno State/ North-East	HIV	150	-Pulmonary aspergillosis (PA) was 12.7% and 11% of these 19 specimens were positive for <i>Aspergillus terreus</i> , 4 (21%) were positive for <i>Aspergillus flavus</i> , 5 (26%) were positive for <i>Aspergillus niger</i> , and 8 (42%) were positive for <i>A. fumigatus</i> . -PA was diagnosed in 12 of 35 participants (34.3%) with CD4+ cell counts <200 cells/ μ l, 5 of 52 (9.6%) with counts of 200–350 cells/ μ l and 2 of 63 (3.2%) with counts >350 cells/ μ l -PA male prevalence was 22.6% and female was 5.7%	38

Table 1 Continued

Study design	City/year	State/Region	subjects	Case(s)	Result highlight(s)	Reference
Cross-sectional study	Owerri, 2020	Imo State/ South-East	HIV subjects	350	-The prevalence of anemia in HIV positive was 44.6% . -The mean hemoglobin statuses at booking was 9.92±1.8g/dl for HIV positive -The mean CD4+ at booking for HIV positive group was 478±251 µl	39
Retrospective study	Port Hacourt, 2021	Rivers States/ South-South	HIV subjects	200	-Overall anaemia was 73.5% in HIV cases with 38% of the cases having mild anaemia, moderate anaemia (25.5%) and 10% had severe anaemia. -The prevalence of leucopenia was 26% and thrombocytopenia (32%). -Haematological indices were WBC 1.3-11.9 x10 ⁹ L, Lymphocyte 0.3-6.4 x10 ⁹ L, Monocyte 0.2-2.6 x10 ⁹ L, Granulocyte 0.1-5.1 x10 ⁹ L and Platelet 30-550 x10 ⁹ L. -HIV infection comes with its health challenges, included anaemia, leukocytopenia, and thrombocytopenia.	17
Retrospective study	Calabar, 2017	Cross State/ South-South	HIV patients	321	-The overall prevalence of anaemia was 76%. -Mild anaemia in female was 57%, moderate anaemia (71.4%) and severe anaemia (55.6%) in HIV subjects -Sex, living in an urban area and low CD4 cell count are risk factors that were associated with anaemia among HIV patients.	40
Retrospective study	Port Hacourt, 2016	Rivers States/ South-South	TB subjects	200	- <i>Candida</i> species prevalence was 25.3% and Male incidence of <i>Candida</i> infections was (27.1%) and female (23.1%).. -The incidence of <i>Candida</i> co-infection was high in TB patients with complications (28.4%) than TB patients with out complications (20%). -The <i>Candida</i> species isolated, <i>Candida albican</i> was 16.3% and most prevalent, followed by <i>Candida tropicalis</i> (8.9%) and <i>Candida stellatois</i> (3.2%).	41
Cross-sectional study	Abuja, 2020	Abuja/ North Central	HIV	420	The overall rate of anaemia was 16.2% while the overall anaemia + malaria co-infection rate was 4.8% in HIV subjects. -Subject history of anaemia, SS blood type, malaria antecedents and normal CD4+ count had higher rates of anaemia and malaria co-infection. -This study highlighted higher rates of malaria co-infection and anaemia among HIV patients.	42

Table 1 Continued

Study design	City/year	State/Region	subjects	Cases	Result highlight(s)	Reference
Retrospective study	Jos, 2016	Plateau State/ North-Central Nigeria	HIV patients	96	-21.9% HIV positive subjects had <i>Candida</i> pathogens 17.7% had <i>Candida albicans</i> isolated from their sputum and 11.5% had a CD4 count of <200 cells/ul. Risk of pulmonary candidiasis occurring in HIV infected patients with CD4count <200cells/ul and <i>Candida species</i> contributed to chronic cough in HIV infected patients.	43

variations in the risk factors common to a particular environment, mode of sample collection/processing after collection and diagnostic approaches used. The high prevalence of 61.7-73.6% observed in some studies conducted in Western and Northern Nigeria may be due to high prevalence of HIV/AIDS patients in the regions and non-compliance of HIV/AIDS subjects to routine medical care/regimens.

The prevalence of fungi isolates was higher in females subject than males in most articles reviewed; especially in Southern and Western Nigeria. This result is concomitant to the finding in South-Western Uganda [9], Calabar [3,19] and Imo State [28]. The high prevalence of fungi isolates in females among HIV/AIDS subjects could be attributed to more females presenting with HIV/AIDS in the hospital settings where this study was conducted. High prevalence of fungi isolates causing mycoses were detected among males subjects than females in Madagascar [1]Northern, Nigeria [2,29, 30, 38], which are not in agreement with our present review study.

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Aspergillus species was the commonest etiologic agent causing mycoses among immuno-compromised subjects in the articles reviewed for this study. This findings is in agreement with the work of Hussein *et al.* in Iraq [48], Punjab, India [49] and Northern Nigeria [29] where *Aspergillus* species was the predominant fungal agent associated with respiratory mycoses among immuno-compromised subjects; followed by *Candida* species. The high prevalence of *Aspergillus* species in these regions of Nigeria may be due to their ability to produce small easily aerosolized conidia which penetrates deep into the lung cavity as previously reported [50]. This study differs from the work in Calabar [3] and in Asia [46] where *Candida* species was the most common aetiologic agent isolated among immuno-compromised subjects with respiratory infections.

Pulmonary mycoses occurred more frequent between 30-40 years; comprising youths and middle aged subjects in majority of the reviewed articles in this current study. This agreed with previously published results in Benin City, Edo State, Nigeria [51], Gombe State [29], Calabar [3,5] and Mbarara, South-Western Uganda [9], where pulmonary mycoses was more prevalent in youths and middle aged individuals. Possible reason for high prevalence within these age brackets may be due to their active outdoor activities leading to exposures of these fungi pathogens [2]. Also another possible reason for this high prevalence of pulmonary mycoses associated with these aged brackets may be related to high unprotected sexual activities in such individuals (youths and middle aged people), as HIV infection primarily occurs through sexual transmission [52].

This study recorded the prevalence 16.2%-75.5% for anaemia among subjects and was more prevalence among females than males subjects. Higher prevalence of 42.2%-97% was documented in Malawi [20] and 38.8-84% in India [53]. The prevalence of 39.5% for anaemia among HIV sero-positive subjects was documented in Javanese, Indonesia [54], 7.2%-84% among subjects living with HIV/AIDS by reviewing documented research in different continents [18], 59.6% in Soweto, South Africa [55], 57.5% before HAART administration in North Eastern Nigeria [56], 63% and 46% before and after HAART administration respectively in Ghana [57] and 40.46% in Tanzania [58]. Additionally, the anaemic prevalence were 31.8-51% in North Central and South-East Ethiopian populations [59-61], 27.6%-44.3% in Chinese populations [62], 20.5% in Rwanda [63], 20.8% in Zauditu [64] and Addis Ababa [65]; both in Ethiopian populations, 12% using subjects from Africa, Asia, South America, Caribbean and United States of America [66], 7.2% in United State of America [67], 6.9% in Denmark [68] and 6.3% in Uganda [69]. The variations in the

prevalence of anaemia in different populations may be due to the sample size of recruited subjects, inclusion and exclusion criteria used in the research methodology, differences in the level of poverty, malnutrition and overall poor economic status of the countries especially in underdeveloped and developing countries [18, 66]. Lower prevalence of anaemia were frequently documented in developed nations among immuno-compromised subjects [67-68], confirming that economic status, good/functional health facilities and good standard of living in a nation contributed to low prevalence of anaemia and mycoses in such developed countries.

5. CONCLUSION

Fungal infections due to immuno-compromised systems of HIV/AIDS, TB and diabetic patients are on the increased. The overall prevalence of anaemia in this study was between 16.2%-75.5% while mycoses prevalence was between 8.7-73.6% among immuno-compromised subjects in reviewed Nigeria populations. Immuno-compromised systems can induce pulmonary mycoses, several hematological manifestations like anemia, neutropenia. Anemia and pulmonary mycoses are treatable comorbidities associated with increased mortality among immuno-compromised subjects; important to clinicians. Hemoglobin levels, platelet and CD4+ T lymphocyte counts should be monitored routinely, especially CD4+ T lymphocyte count of <200 cells/ μ l.

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