

RESEARCH NOTE

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Severe anaemia in people with HIV: demographic, clinical and renal correlates

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Abstract

Objective This study aimed to investigate the sociodemographic, clinical and renal correlates associated with severe anaemia among people with HIV.

Methods We conducted a cross-sectional analysis of people with HIV on antiretroviral therapy (ART) for at least 6 months, stratified by anaemia status. Anaemia was defined based on the World Health Organisation (WHO) classification, as haemoglobin concentration lower than normal i.e. <12 g/dl in females and <13 g/dl in males and the primary outcome, severe anaemia, as a haemoglobin level below 8 g/dl according to the World Health Organisation.

Results The study comprised 372 participants receiving ART, of whom 236 (63.4%) were females. The mean age \pm SD of the participants was 44.8 ± 12.4 years. The overall prevalence of severe anaemia was 7.8% (95% CI: 0.053–0.111). In multivariable logistic regression analysis, factors significantly associated with severe anaemia were female sex (Adjusted Odds Ratio (AOR: 14.3, 95% CI: 2.14–126.6), albumin (AOR: 0.93 95% CI: 0.88–0.98) and creatinine levels (AOR: 1.01 95% CI: 1.00–1.03).

Keywords Severe anaemia, Renal insufficiency, PLWH, ART

Introduction

Severe anaemia is a serious comorbidity of HIV which can rapidly complicate the quality of life and disease prognosis [1, 2]. The risk of mortality increases significantly with more severe forms of anaemia [3–5]. Even with effective antiretroviral therapy (ART), the challenge of severe anaemia in People living with HIV (PLWH) persists [6–8], highlighting the need for further inquiry. While the direct impact of HIV on haematopoiesis is

well-documented, other contributing factors such as opportunistic infections, nutritional deficiencies, and prolonged HIV medications may further complicate the pathophysiology of anaemia in PLWH [9, 10]. Furthermore, socio-economic factors and limited health-care access can exacerbate the risk of severe anaemia in PLWH.

Reduced erythropoietin production, impaired iron utilization, and inflammation contribute to anaemia in these patients. Investigating the mechanisms associated with severe anaemia is essential for targeted interventions [11]. Renal insufficiency, a common comorbidity in HIV, can lead to reduced erythropoietin production and subsequent anaemia, further complicating the clinical management. Despite the recognition of this clinical entity, there remains a paucity of literature specifically addressing severe anaemia among treated PLWH. This study

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aimed to investigate the correlates of severe anaemia in PLWH.

Materials and methods

Study design and setting

This was a cross-sectional study among adult PLWH who had been on ART for at least 6 months or more, between 1st September 2023 and 26th February 2024 at Livingstone University Teaching Hospital (LUTH) a referral hospital in the southern part of Zambia.

Eligibility criteria

We recruited adult PLWH aged 18 years and above who had been receiving ART for ≥ 6 months. In this study, pregnant women, participants with excessive menstrual bleeding and malignant neoplasms were excluded.

Sample size calculation

PLWH on treatment is 3880 at LUTH ART Clinic, we hypothesized a maximum percentage prevalence of 50% and 95% confidence level, and we used an online OpenEpi software [12]. We accounted for missing data by adding a 30% contingency, the final determined sample size was 372.

Study variables and definitions

Sociodemographic data, including age, sex, blood pressure, alcohol use and physical exercise were collected from participants and health records (SmartCare and patient files) using a structured questionnaire and data collection form.

Kidney function (eGFR) was assessed according to the simplified version of the Modification of Diet in Renal Disease (MDRD) study equation: $186 \times \text{SCr}(\text{mg/dl})^{-1.154} \times \text{age}(\text{years})^{-0.203} \times 0.742$ (if female) $\times 1.210$ (as our population are Africans) [13]. Staging of renal function was based on the National Kidney Foundation Disease Outcomes Quality Initiative (K/DOQI) classification [14]. Normal renal function was defined as normal or increased eGFR ($\text{eGFR} \geq 90 \text{ ml/min/1.73 m}^2$) [14]. Mild, moderate, and severe renal impairment were defined as eGFR 60–89.9, 30–59.9 and 15–29.9 ml/min/1.73 m^2 , respectively. Impaired renal function was defined as $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ [12]. Furthermore, anaemia was defined based on the World Health Organisation (WHO) classification, as haemoglobin concentration lower than normal i.e. $< 12 \text{ g/dl}$ in females and $< 13 \text{ g/dl}$ in males. Further sub-classified the anaemia as mild (11–12.9 g/dl for males and 11–11.9 g/dl for females), moderate (8–10.9 g/dl) and severe ($< 7.9 \text{ g/dl}$) [15].

Primary outcome Severe anaemia was defined as a Haemoglobin level below 8 g/d based on the World Health Organisation criteria [15].

Blood samples and measurements

Viral load and CD4 lymphocyte count samples were collected in ethylenediaminetetraacetic acid (EDTA) containers; Becton Dickson (BD) flow cytometer was used to analyse total lymphocyte and CD4 lymphocyte count, while viral load was analysed using Ampliprep/Taqman 96 PCR analyzer. Haemoglobin (Hgb) and full blood count values were determined using the haematology analyzer Sysmex XT2000 (Abbott Laboratories Diagnostics Division, USA) and CD4+ T cells were assayed using the BD FACSCOUNT system (Becton Dickinson and Company, California, USA). Biochemical analyses were done on a Pentra C200 and HumaStar 80 clinical chemistry analyzer (Human Diagnostics, Germany) using kits supplied by the manufacturer.

ART regimens

Protease inhibitor regimens consist of either lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r) combined with one of the following NRTI combinations: ABC/XTC, zidovudine/XTC (AZT/XTC), or TDF/XTC. NNRTI regimens include efavirenz (EFV) or nevirapine (NVP) combined with either Abacavir and lamivudine/emtricitabine (ABC/XTC) or tenofovir disoproxil fumarate and lamivudine/emtricitabine (TDF/XTC). An INSTI regimen comprises Dolutegravir (DTG) combined with TDF/lamivudine (TDF/3TC).

Statistical analysis

SPSS version 22 was used for statistical analysis. Categorical data were summarized with frequencies and proportions, and continuous variables with medians and interquartile ranges (IQR) due to non-normal distribution, confirmed via Q-Q plots and the Shapiro-Wilk test. The Pearson chi-square test assessed significant associations between categorical variables. We compared the groups using one-way ANOVA for normally distributed variables, or otherwise using the Kruskal-Wallis test for variables that were not normally distributed. Logistic regression (univariable and multivariable) was utilized to estimate factors associated with severe anaemia. Covariates included in the final model were selected based on published evidence and variables found to be statistically significant in univariable analysis.

Ethical considerations

Ethical approval for the study was obtained on 7th August 2023 from the University of Zambia Biomedical Research Ethics Committee (UNZABREC- REF. REF. NO. 4062 – 2023). The purpose of the study was explained to all the participants in a language familiar to them, and they provided written informed consent after agreeing to take part in the study. The research was conducted in accordance with the Declaration of Helsinki on ethical

principles for medical research involving human subjects [16] and relevant local regulations and guidelines.

Results

Sociodemographic and clinical characteristics of the study participants

The study comprised 372 participants receiving ART, of whom 236 (63.4%) were females. The mean age \pm SD of the participants was 44.8 ± 12.4 years, with a range of 18 to 79 years. The overall prevalence of severe anaemia was 7.8% (95% CI: 5.3–11.1). Furthermore, a significant proportion of participants reported alcohol consumption (210, 56.8%). Additionally, 12.2% (45/370) of participants were hypertensive, while 28.4% (105 out of 370) engaged in regular physical exercises. In terms of ART regimens, the majority of patients were on NNRTI-based regimens ($n=258$, 69.7%), followed by INSTI-based regimens ($n=65$, 17.6%).

Relationship of anaemia status with demographic and clinical factors

The baseline characteristics of patients stratified by anaemia status among PLWH. It reveals significant associations between anaemia severity and various demographic, clinical, and lifestyle factors. A higher prevalence of anaemia is observed among females compared to males (Fig. 1A). Additionally, significant differences based on ART regimens are evident across anaemia categories (Fig. 1C). Lifestyle factors such as physical exercise (Fig. 1D) and alcohol consumption also demonstrate significant associations with anaemia levels. Furthermore, differences in clinical parameters including albumin levels, CD4 counts, creatinine levels, and duration of ART highlighted the significant differences with the anaemia categories in treated HIV patients, Table 1.

Renal insufficiency and anaemia prevalence in PLWH

In our study, we observed varying degrees of renal insufficiency among the participants. Specifically, 166 individuals (44.8%) had normal kidney function, 175 (47.4%) had mild insufficiency, 27 (7.3%) had moderate insufficiency,

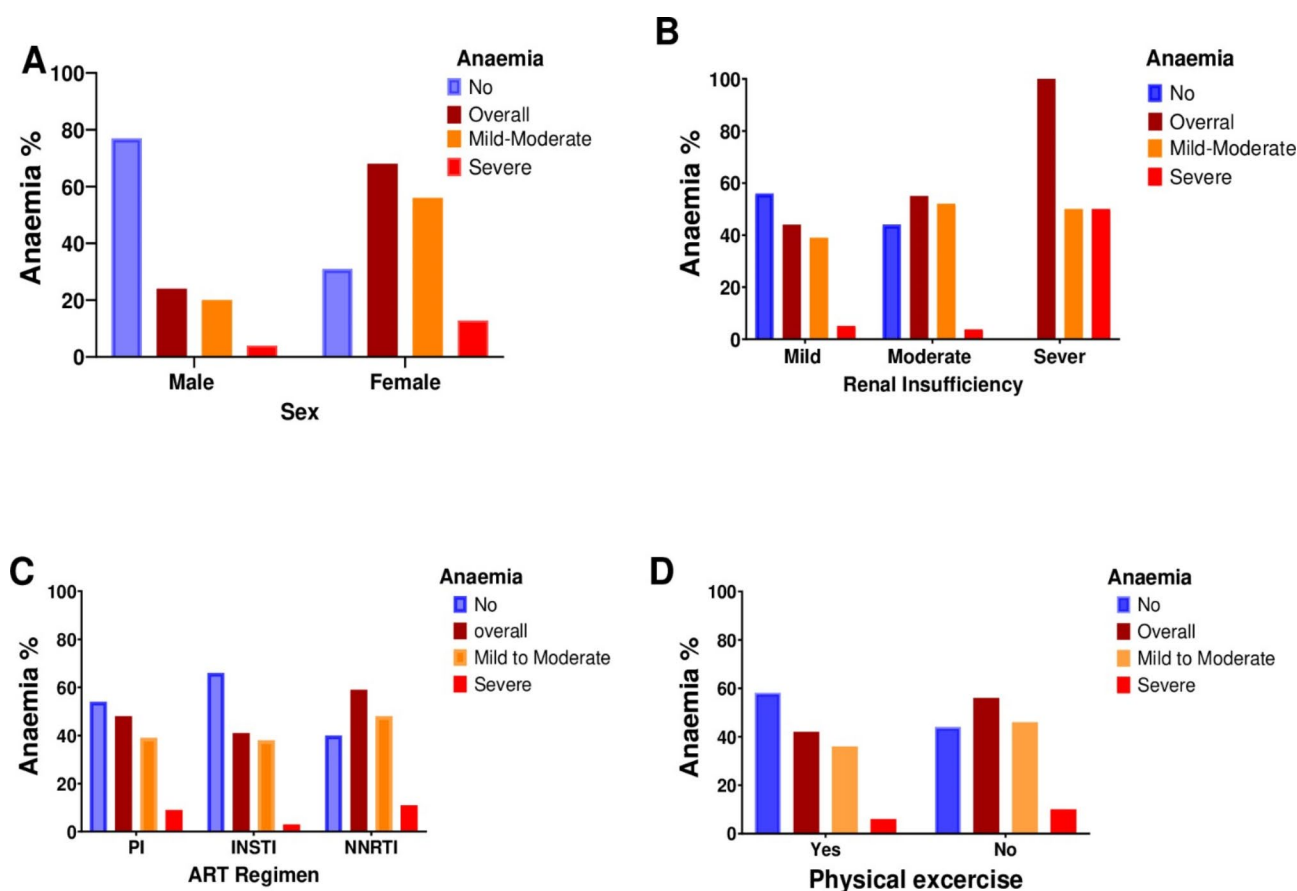


Fig. 1 Prevalence of anaemia and Severity based on Sex, Renal insufficiency, ART Regimens and Physical exercise. ART Antiretroviral therapy, PI Protease Inhibitor, INSTI Integrase Strand Transfer Inhibitor, NNRTI Non Nucleoside Reverse Transcriptase Inhibitor, $P < 0.05$

Table 1 Baseline characteristics of the patients according to haemoglobin levels he patients according to haemoglobin levels

Variable	Total	Anaemia Status			P-value
		No Anaemia	Mild-Mod	Severe	
Age Mean SD	372	44.7 ± 12.1	45.4 ± 12.5	43.7 ± 13.9	0.464
Sex					< 0.001
Male	136	104 (76.5)	27 (19.9)	5 (3.7)	
Female	234	72 (30.8)	132 (56.4)	30 (12.8)	
Total	370	176	159	35	
Regimen	n = 369				0.016
PI	46	25 (54.3)	18 (39.1)	4 (8.7)	
INSTI	65	43 (66.2)	20 (30.8)	2 (3.1)	
NNRTI	258	108 (40.3)	121 (47.5)	29 (11.2)	
Total	369	176	159	35	
Physical exercise					0.035
Yes	105	61 (58.1)	38 (36.2)	6 (5.7)	
No	261	114 (41.1)	120 (46.7)	27 (10.3)	
Total	366	175	158	33	
Alcohol n = 366					0.002
Yes	210	117 (55.7)	76 (36.2)	17 (8.1)	
No	159	59 (37.1)	82 (51.6)	18 (11.3)	
total	369	176	158	35	
Renal Insufficiency	n = 367				< 0.001
Normal	164	64 (39)	78 (47.6)	22 (13.4)	
Mild	174	98 (56.3)	70 (40.2)	6 (3.4)	
Moderate	27	12 (44.4)	15 (55.6)	0 (0)	
Severe	2	0 (0)	1 (50)	1 (50)	
Total	367	174	164	29	
Alt U/L	361	15 (13, 27)	19.7 (16, 26)	16.9 (12, 26)	0.16
Albumin g/dl	288	42.4 (39, 46)	41.9 (37, 44)	40.7 (34, 43)	0.009
Ast U/L	365	31.1 (26, 40)	30.4 (24, 43)	30.8 (23, 40)	0.92
CD4 + t (cells/mL) m(IQR)	371	611 (394, 806)	665 (363, 906)	453 (325, 805)	0.009
Creatinine mg/dL	369	81.6 (70, 97)	76.8 (67, 90)	70.1 (66, 80)	0.002
Duration ART mo, m(IQR)	372	61 (8.5, 65.5)	66.5(31, 71)	64 (30.5, 73)	0.02
VL(copies/mL)	372	0 (0, 20190)	0 (0, 84)	20 (0, 91)	0.92
BMI kg/m ² , m(IQR)	372	21.7 (18, 28)	22.1 (19, 24)	22.6 (20, 27)	0.77
MAP mmHg	372	87.2 (80, 99)	82.8 (79, 89)	84.3 (77, 92)	< 0.001
Weight m, IQR	372	55 (49, 70)	58.5 (52, 64)	63 (52, 69)	0.014
eGFR mL/min	369	80 (62, 92)	90 (80, 103)	99 (90, 116)	0.008
MCV fl.	371	98 (92.5, 103)	95.7(89, 101)	91 (71.8, 96.5)	0.051

Values are presented as mean ± standard deviation for the continuous variables and frequency (percentage) for the categorical variables

eGFR: estimated glomerular filtration rate, MCV: mean corpuscular volume, FBS: Fasting blood sugar, VL: Viral load, ESR: erythrocyte sedimentation rate, NNRTI = non-nucleoside/nucleotide reverse transcriptase inhibitor (EFV = efavirenz and NVP = Nevirapine), PI = protease inhibitor (LPV/r = lopinavir/ritonavir and ATV/r = atazanavir/ritonavir), INSTI = integrase strand transfer inhibitor (DTG = dolutegravir), NRTI = nucleotide reverse transcriptase inhibitor

and 2 (0.5%) had severe insufficiency based on their estimated glomerular filtration rate (eGFR) values. As renal function declines, from mild renal insufficiency to severe renal insufficiency, there is a corresponding increase in the prevalence of anaemia (Fig. 1B). Severe anaemia was more prevalent in patients with severe renal insufficiency 50%, followed by mild renal insufficiency 5% (Fig. 1B). The prevalence of overall anaemia among participants with impaired renal function (eGFR < 60 mL/min/1.73 m²) was higher (44.8%) than those without impaired renal function (35.6%, $p = 0.32$).

Factors associated with severe anaemia

In the unadjusted analysis (Table 2), several factors were found to be associated with severe anaemia in PLWH. Female participants had significantly higher odds of severe anaemia compared to males (OR = 3.95, 95% CI: 1.34–11.59, $p = 0.013$). Lower albumin levels were also associated with an increased risk of severe anaemia (OR = 0.95, 95% CI: 0.91–0.99, $p = 0.024$). Mean arterial pressure (MAP) showed a marginal association, with lower MAP increasing the odds of severe anaemia (OR = 0.96, 95% CI: 0.93–0.99, $p = 0.023$). Estimated glomerular filtration rate (OR = 1.01, 95% CI: 0.99–1.02,

Table 2 Factors associated with severe anaemia

Variables	Unadjusted analysis			Adjusted analysis		
	OR	95%CI	P value	AOR	95%CI	P-value
Age Mean, SD	0.99	0.96–1.02	0.57	0.98	0.94–1.01	0.195
Sex						
Male	1					
Female	3.947	1.34–11.59	0.013	16.45	2.14–126.50	0.007
Albumin g/dL	0.949	0.91–0.99	0.024	0.93	0.88–0.98	0.014
Creatinine mg/dL	1.001	0.99–1.01	0.878	1.01	1.00–1.03	0.031
VL copies/mL	1.00	1.00–1.00	0.60	1.00	1.00–1.00	0.891
CD4+ count cells/mL	0.99	0.99–1.0	0.14	0.99	0.99–1.00	0.241
BMI kg/m ²	0.96	0.88–1.04	0.29	0.98	0.86–1.10	0.697
MAP mmHg	0.96	0.93–0.99	0.023	0.97	0.93–1.01	0.150
eGFR mL/min	1.01	0.99–1.02	0.25			

OR; odds ratio, CI; confidence interval, AOR; adjusted odds ratio SD; Standard deviation; VL; Viral load; BMI; Body Mass Index, MAP; Mean Arterial Pressure, CD4; Cluster of differentiation, eGFR; Estimated Glomerular Filtration Rate

$p=0.25$) was also included in the univariate model, but it did not emerge as a significant factor. Other variables, including age, viral load, CD4+ count, BMI and creatinine, did not show significant associations in the unadjusted analysis.

In the adjusted analysis (Table 2), Female sex remained a significant predictor of severe anaemia, with the odds increasing substantially after adjustment (AOR=16.45, 95% CI: 2.14–126.50, $p=0.007$). Lower albumin levels continued to show a significant association with severe anaemia (AOR=0.93, 95% CI: 0.88–0.98, $p=0.014$), while creatinine gained significance after adjusting for other variables (AOR=1.01, 95% CI: 1.00–1.03, $p=0.031$). Other variables such as age, viral load, CD4+ count, BMI, and MAP did not show significant associations after adjustment.

Discussion

This study sought to evaluate the sociodemographic, clinical, and renal factors associated with severe anaemia in PLWH. In this study, we observed an 7.8% prevalence of severe anaemia. Factors significantly associated with severe anaemia included female sex, albumin levels, and creatinine levels. Severe anaemia complicates the management of PLWH, presenting multifaceted challenges to clinicians especially when associated with renal insufficiency. Our findings show that as renal function declines from mild to severe renal insufficiency, there is a corresponding increase in the prevalence and severity of anaemia. Similar with findings elsewhere, our results suggest that HIV infection and renal insufficiency interact to exacerbate anaemia and its severity [13, 17]. Females exhibited significantly higher odds compared to males, consistent with previous studies demonstrating sex-based disparities in anaemia prevalence [18–20].

We also found that low Albumin is associated with severe anaemia in PLWH. Albumin is a marker of nutritional status, and transporting essential nutrients,

including vitamins and minerals, which are necessary for erythropoiesis [21]. Low albumin levels may indicate increased catabolism and malnutrition, which is a known risk factor for anaemia [22]. Moreover, albumin serves as a negative acute-phase reactant, as its levels decrease during inflammatory states, which can suppress erythropoiesis [23–25]. Additionally, higher creatinine levels were significantly associated with severe anaemia in our study [26]. Elevated creatinine reflects impaired renal function contributing to the prevalence of anaemia [27]. Our study shows that renal insufficiency is prevalent among PLWH, can impair erythropoietin production subsequently hindering erythropoiesis and causing anaemia [28, 29].

Despite the insights provided by this study, several limitations warrant consideration. The cross-sectional design precludes causal inference. In addition, the low number of the outcome variable (severe anaemia) may have resulted in wider confidence intervals, reducing the precision of the estimates in the regression analysis.

In conclusion, severe anaemia represents a significant challenge in the management of HIV-infected individuals. Factors such as female sex and creatinine levels, and decreased albumin levels emerged as significant factors associated with severe anaemia, highlighting the multifactorial nature of this complication. Screening for anaemia and renal function should be integrated into routine HIV care, to improve patient outcomes.

Author contributions

K.K., B.M.H., S.K.M. conceptualized the study and wrote the main manuscript. B.M.H., S.M.M., M.M. and JAM edited different sections of the manuscript. K.K. created all the figures and tables. K.K., CNP, S.M.M. and S.K.M. finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This study received no external funding to conduct this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Received: 17 May 2024 / Accepted: 10 January 2025

Published online: 03 February 2025

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