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Factors Associated with Anemia in HIV-infected Individuals in Southern India

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Summary

Anemia accelerates disease progression and increases mortality among HIV-infected individuals. Few studies have characterized this problem in developing countries. Hemoglobin values of adults presenting to an HIV tertiary care center in India between 1996 and 2007 were collected (n=6996). Multivariate logistic regression analysis was performed to examine associations among anemia, HIV progression, and co-morbidities. Overall anemia prevalence was 41%. Twenty percent of patients with CD4 counts >500 cells/μL were anemic, compared to 64% of those with CD4 counts <100 cells/μL ($p<0.001$). In multivariate analysis, CD4 count <100 cells/μL (OR:5.0, CI:4.0–6.3), underweight body-mass index (OR:4.8, CI:3.6–6.5), female gender (OR:3.1, CI:2.8–3.6), and tuberculosis (OR:1.6, CI:1.4–1.8) were significantly associated with anemia. In this setting, management of anemia should focus on antiretroviral therapy, nutritional supplementation, and tuberculosis control. The high anemia prevalence among patients meeting criteria for antiretroviral therapy highlights the need for increased access to non-AZT nucleoside reverse transcriptase inhibitors in developing countries.

Keywords

anemia; HIV; tuberculosis; India; malnutrition; resource-limited settings

Introduction

Anemia is the most common hematological complication associated with HIV, with rates increasing with disease progression.[1] Anemia is independently associated with decreased quality of life, accelerated disease progression, and increases mortality in HIV-infected individuals.[2,3] Survival time in HIV-infected individuals may be improved with recovery

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from anemia.[1] By adversely affecting quality of life, anemia may exacerbate poverty in communities with high HIV prevalence.[4]

In developing countries such as India, where more than half of women in the general population are anemic,[5] the interaction between HIV and anemia may be even more detrimental. Estimates of the prevalence of anemia among HIV-infected individuals in sub-Saharan Africa range from 70–90%,[3,6–8] as compared to 20–60% in reports from developed countries. [1,9] Few studies have examined factors associated with anemia in developing country settings. Risk factors for anemia in developing countries may vary from those in developed countries due to endemic malnutrition, helminth infections, tuberculosis (TB), malaria, and a different spectrum of opportunistic infections. Here we report the prevalence of, and factors associated with, anemia among HIV-infected individuals at an HIV/AIDS tertiary care center in South India.

Methods

The Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE) is an HIV tertiary care clinic in Chennai, India, which has provided medical care to nearly 10,000 patients since 1994. Analysis was done using the YRG CARE HIV Natural History Study Observational Database, which has been previously validated and approved by YRG CARE's independent institutional review board.[10] This database captures demographic and clinical details (including CD4 cell counts, hemoglobin values, opportunistic infections, and HIV-related co-morbidities) from every patient visit. Patients greater than 18 years of age who visited between January 1, 1996 and December 31, 2006 were included. Only baseline hemoglobin values ordered at the time of a patient's initial enrollment for care were analyzed.

Anemia was classified by the following WHO criteria for both men and women: "non-anemic" (hemoglobin value ≥ 11 g/dL), grade one (9.5–10.9 g/dL), grade two (8–9.4 g/dL), grade three (6.5–7.9 g/dL), and grade four (<6.5 g/dL). For comparison with other studies, anemia was also reclassified as hemoglobin values <12 g/dL for women and <13 g/dL for men as noted in the discussion. Body-mass index (BMI) values, CD4 cell counts, and HIV-associated co-morbidities recorded or diagnosed at the time of enrollment into care were included in the analysis.

Statistical analyses were performed with SPSS (version 10.0.5; Chicago, IL). Normal data were summarized using mean and standard deviation (SD) and non-normal data using median and interquartile range (IQR). Student's t-test was used to compare the mean hemoglobin values of the various CD4 cell count strata. Trends in anemia grades among the different CD4 cell count strata were tested using χ^2 for trend with Epi Info (version 3.3.2, CDC, Atlanta, GA). Univariate and multivariate logistic regression were performed to understand the associations between anemia and the various demographic and clinical characteristics. Statistically significant variables ($p<0.05$) were included in the multivariate model using the forward stepwise method, and the best reduced model was built based on a 2 log likelihood value.

Results

In this analysis, 6996 patients who were over 18 years of age and had a hemoglobin value recorded at the time of enrollment into care were included, of whom 70% were male and 96% had acquired HIV through heterosexual transmission. Those without a hemoglobin value recorded at the time of enrollment into care, 2648 patients (27.5%), were excluded from all analyses. Male-female ratio, mean age, and mean BMI between the included and excluded groups were similar. Specifically, patients included in the analysis had a 70% male predominance, a mean age of 33.6 years (SD 8.3), and a mean BMI of 20.1 (SD 2.8); this compares to a 63% male predominance, a mean age of 32.2 year (SD 8.0), and a mean BMI of 20.0 (SD 3.9) in the group excluded from the analysis.

The mean hemoglobin value for the entire cohort was 11.4 g/dL (SD:2.5). Using the WHO definition of anemia, 41% of the cohort was anemic, with 19% having grade one, 13% having grade two, 6% having grade three, and 3% having grade four anemia. Among the 4431 patients with CD4 cell count values available, the mean hemoglobin value declined from 12.6 g/dL at CD4 cell counts >500 cells/μL to 10.0 g/dL at CD4 cell counts <100 cells/μL (p-value for trend <0.001, Figure 1). The percent of non-anemic individuals decreased from 80% at CD4 cell counts >500 cells/μL to 36% at CD4 cell counts <100 cells/μL (p<0.001, Figure 1). There was a corresponding statistically significant increase in the percentage of patients with all grades of anemia with declining CD4 cell count (Figure 1). Using the alternative definition of anemia as any hemoglobin value <12 g/dL for women and <13 g/dL for men, 69% of the entire cohort (72% of women and 67% of men) and 89% of patients with a CD4 cell count <100 cell/μL were anemic.

In the multivariate model, CD4 cell count <100 cells/μL and underweight BMI were both associated with an approximately five times increased adjusted odds of anemia (Table 1). Female gender, extrapulmonary TB, and pulmonary TB also had strong independent associations with anemia. Age >31 years, oral and esophageal candidiasis, and generalized lymphadenopathy had milder independent associations with anemia.

Discussion

This study highlights the high prevalence of anemia in HIV-infected individuals in south India, especially among immunosuppressed patients. Using a definition of anemia as any hemoglobin value <12 g/dL for females and <13 g/dL for males, other developing country studies found a 70–90% anemia prevalence among HIV-infected individuals, which is similar to the 69% found in our study.[3,6–8] The 72% prevalence of anemia among women in this study is significantly higher than the 50–57% prevalence in large-scale surveys of women from the general population of the two south Indian states from which our clinic derives its patient population.[5] Most developing country studies have focused specifically on HIV-infected groups at higher risk for anemia, such as pregnant or TB co-infected patients. Since this study has patients of both genders distributed across all CD4 cell count strata, it may more accurately reflect the prevalence of anemia among HIV-infected individuals in India.

In our study, the influence of HIV disease on anemia starts well before patients are eligible for HAART, with a significant increase in anemia evident even at CD4 cell counts of 201–350 cells/μL. Similar to prior findings, a low CD4 cell count has a strong independent association with anemia even after controlling for opportunistic infections and malnutrition.[1,11] This association may represent anemia caused by the HIV virus itself, which may inhibit hematopoiesis directly through infection of progenitor cells or upregulation of cytokines.[8] Studies from developed countries suggest that HAART resolves anemia in many patients, which is consistent with our finding that immunosuppression makes a strong independent contribution to anemia.[9,12] While a preliminary analysis from our clinic suggests a similar trend of anemia resolution with HAART,[13] further prospective data is needed to answer this important question in developing countries.

The association of anemia with low BMI is of specific relevance to India, where the rate of chronic malnutrition is among the highest in the world.[14] Interestingly, even individuals with a normal BMI had a two and a half times increased odds of anemia as compared to those who were overweight. Low BMI is associated with many nutrient deficiencies—including iron, folate, and B12—that contribute directly to anemia. The increased independent odds of anemia with candida infection may also reflect micronutrient deficiency, since both oral and esophageal infection decrease oral intake.

As TB is the second most common opportunistic infection in India (after oral candidiasis),[15] it may greatly exacerbate the burden of anemia in this population. The etiology of anemia in TB is multifactorial, resulting from a combination of anemia of chronic disease and deficiencies of nutrients such as iron, vitamin A, and selenium.[6] The increased odds of anemia in females most likely reflects the high rate of iron deficiency in Indian women due to menstrual blood loss, poor nutritional status, and pregnancy.[5] Three of the strongest factors associated with anemia— TB , immunosuppression, and malnutrition—exacerbate each other in synergistic manner. The net result is a vicious cycle placing HIV-infected patients in TB-endemic countries at very high risk for developing anemia.[6,7] Therefore, in addition to roll-out of HAART, nutritional support and aggressive TB control should be the cornerstones of anemia management for HIV-infected individuals in India.

The main limitation of this analysis is its cross-sectional design, which precludes definite determination of the temporal relationships between anemia and its associated factors. Also, our database does not capture laboratory findings (i.e., mean corpuscular volume, iron studies, etc.) that could clarify the frequency of anemia due to particular nutrient deficiencies.

Finally, the high prevalence of anemia in patients with CD4 cell counts <200 cells/μL has implications for the choice of initial HAART regimen in developing countries. Since anemia is an adverse effect of zidovudine (AZT), use of this drug is contraindicated in patients with preexisting anemia.[16,17] Therefore, more than half of patients who meet criteria for HAART in this setting would not be eligible for initiation on regimen that includes AZT. This highlights the need for increased access to NRTIs with different toxicity profiles, such as tenofovir and abacavir, in resource-limited settings.

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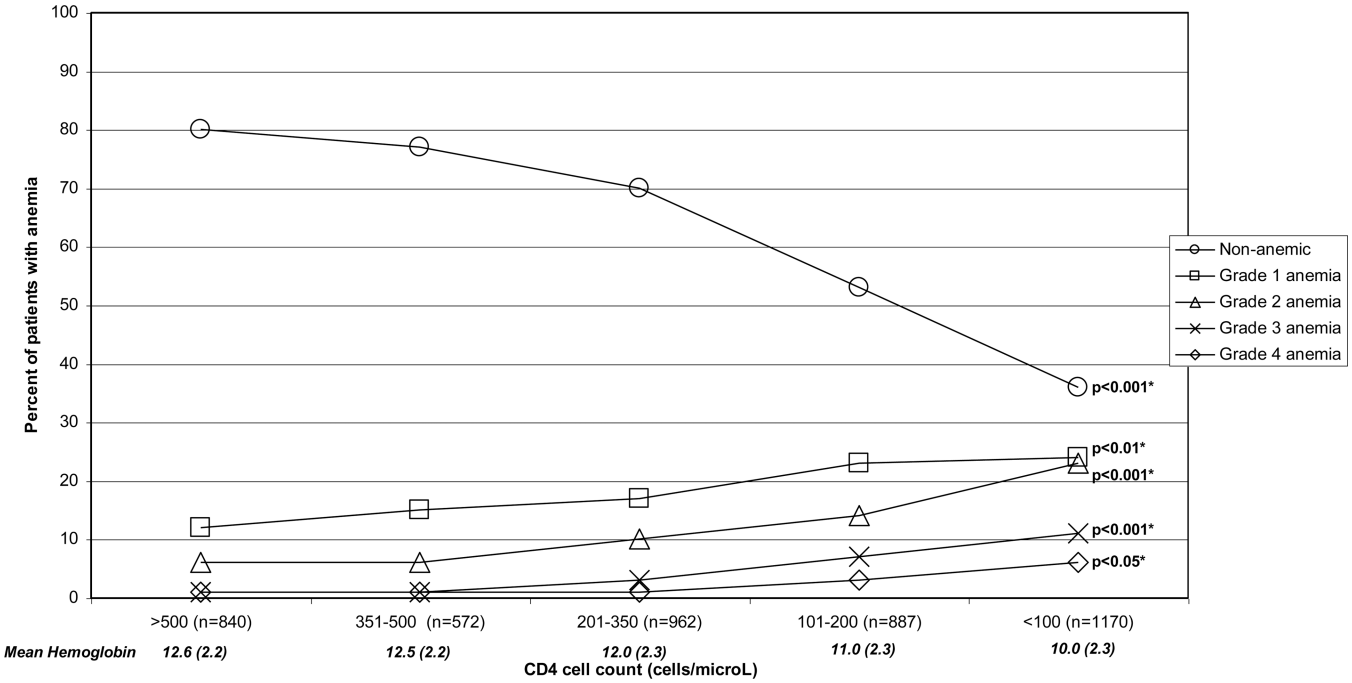

Figure 1.

Influence of HIV disease progression on anemia and mean hemoglobin

* p-value of χ^2 for trend

Table 1

Factors Associated with Anemia in Univariate and Multivariate Analyses

Risk factor	Non-anemic N (%)	Anemic N (%)	Univariate Odds Ratio (CI)	Multivariate Odds Ratio (CI)
Gender				
Male	3105 (75)	1820 (64)	1.0	1.0
Female	1052 (25)	1019 (36)	1.7 (1.5–1.8)	3.1 (2.8–3.6)
Age				
18–30	1764 (42)	1088 (38)	1.0	1.0
31–50	2231 (54)	1624 (57)	1.2 (1.1–1.3)	1.1 (1.02–1.3)
>50	162 (4)	127 (5)	1.3 (1.0–1.6)	1.4 (1.07–1.9)
Body Mass Index (kg/m^2)				
>25	409 (10)	63 (2)	1.0	1.0
18.5–24.9	1534 (37)	704 (25)	3.0 (2.3–3.9)	2.5 (1.9–3.4)
<18.5	933 (22)	972 (34)	6.8 (5.1–8.9)	4.8 (3.6–6.5)
Not available	1281 (31)	1100 (39)	--	--
CD4 cell count (cells/μL)				
>500	673 (16)	167 (6)	1.0	1.0
351–500	440 (11)	132 (5)	1.2 (0.9–1.6)	1.1 (0.9–1.5)
201–350	665 (16)	297 (11)	1.8 (1.4–2.2)	1.6 (1.3–2.1)
101–200	469 (11)	418 (15)	3.6 (2.9–4.5)	2.7 (2.1–3.4)
0–100	421 (10)	749 (26)	7.2 (5.8–8.8)	5.0 (4.0–6.3)
Not available	1489 (36)	1076 (38)	--	
Pulmonary tuberculosis				
No	3338 (80)	1784 (63)	1.0	1.0
Yes	819 (20)	1055 (37)	2.4 (2.2–2.7)	1.6 (1.4–1.8)
Extrapulmonary TB				
No	4023 (97)	2528 (89)	1.0	1.0
Yes	134 (3)	311 (11)	3.7 (3.0–4.5)	2.5 (2.0–3.1)
Candidiasis (Oral and Esophageal)				
No	3109 (75)	1594 (56)	1.0	1.0
Yes	1048 (25)	1245 (44)	2.3 (2.1–2.6)	1.5 (1.3–1.7)
PCP				
No	4071 (98)	2695 (95)	1.0	1.0
Yes	86 (2)	144 (5)	2.5 (1.9–3.3)	1.3 (0.97–1.7)
Cryptococcal meningitis				
No	4121 (99)	2801 (99)	1.0	
Yes	36 (1)	38 (1)	1.6 (0.98–2.46)	
Cytomegalovirus retinitis				
No	4140 (99.5)	2812 (99)	1.0	1.0
Yes	17 (0.4)	27 (1)	2.3 (1.3–4.3)	1.4 (0.7–2.7)
Oral hairy leukoplakia				
No	4072 (98)	2776 (98)	1.0	

Risk factor	Non-anemic N (%)	Anemic N (%)	Univariate Odds Ratio (CI)	Multivariate Odds Ratio (CI)
Yes	85 (2)	63 (2)	1.1 (0.8–1.5)	
Lymphadenopathy				
No	3891 (94)	2492 (88)	1.0	1.0
Yes	266 (6)	347 (12)	2.0 (1.7–2.4)	1.6 (1.3–1.9)
Herpes zoster				
No	3610 (87)	2474 (87)	1.0	
Yes	547 (13)	365 (13)	1.0 (0.8–1.1)	
Herpes simplex				
No	3973 (96)	2694 (95)	1.0	
Yes	184 (4)	145 (5)	1.2 (0.9–1.5)	
Chronic diarrhea				
No	4014 (97)	2671 (94)	1.0	1.0
Yes	143 (3)	168 (6)	1.8 (1.4–2.2)	1.3 (1.0–1.7)
Bacterial infections of the skin				
No	4144 (99.7)	2829 (99.6)	1.0	
Yes	13 (0.3)	10 (0.4)	1.1 (0.5–2.6)	
Fungal Skin Infections				
No	4069 (98)	2789 (98)	1.0	
Yes	88 (2)	50 (2)	0.8 (0.6–1.2)	
Ascites				
No	4153 (99.9)	2824 (99.5)	1.0	1.0
Yes	4 (0.1)	15 (0.5)	5.5 (1.8–16.5)	2.4 (0.7–8.0)
Renal Disease				
No	4120 (99)	2807 (99)	1.0	
Yes	37 (1)	32 (1)	1.3 (0.8–2.0)	
Syphilis				
No	4150 (99.8)	2838 (100)	1.0	
Yes	7 (0.2)	1 (0)	0.2 (0.03–1.7)	
Malaria				
No	4150 (99.8)	2830 (99.7)	1.0	
Yes	7 (0.2)	9 (0.3)	1.9 (0.7–5.1)	