Original Article

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A cross-sectional study of leukopenia and thrombocytopenia among Chinese adults with newly diagnosed HIV/AIDS

Yinzhong Shen[1,2], Jiangrong Wang[2], Zhenyan Wang[2], Jiayin Shen[2], Tangkai Qi[2], Wei Song[2], Yang Tang[2], Li Liu[2], Renfang Zhang[2], Yi Zeng[1], Hongzhou Lu[2,*]

[1] *College of Life Science and Bioengineering, Beijing University of Technology, Beijing, China;*
[2] *Department of Infectious Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China.*

Summary **We conducted a cross-sectional study to determine the prevalence and risk factors of leukopenia and thrombocytopenia among Chinese adults with newly diagnosed HIV/AIDS. One thousand nine hundred and forty-eight newly diagnosed HIV-infected patients were enrolled between 2009 and 2010. Serum samples obtained from each individual were collected for complete blood count. Factors associated with the presence of leukopenia and thrombocytopenia were analyzed by multiple logistic regression. The overall prevalence of leukopenia and of thrombocytopenia was 33.2% and 15.6%, respectively. The prevalence of leukopenia was higher among females than among males (39.4% *versus* 31.2%). The prevalence of leukopenia increased with decreasing CD4 count (8.2%, 26.5%, 33.4%, and 41.5% among patients with CD4 count of ≥ 350, 200-349, 50-199, and < 50 cells/mm^3 respectively). The prevalence of thrombocytopenia also showed an increasing trend with decreasing CD4 count (5.8%, 12.2%, 17.8%, and 17.5% among patients with CD4 count of ≥ 350, 200-349, 50-199, and < 50 cells/mm^3, respectively). Logistic analysis showed that female sex, lower CD4 count, and Han ethnicity were significantly associated with an increased risk of leukopenia, and that lower CD4 count, and HIV transmission by blood were significantly associated with an increased risk of thrombocytopenia. The study reflects that leukopenia and thrombocytopenia are common among Chinese adults with newly diagnosed HIV/AIDS; and lower CD4 count is associated with an increased risk of both leukopenia and thrombocytopenia. We propose that a routine assessment of these parameters is necessary for timely and adequate clinical management.**

Keywords: Acquired immune deficiency syndrome, leukopenia, thrombocytopenia, prevalence, risk factor, CD4$^+$T lymphocyte count

1. Introduction

Hematologic abnormalities, which involved all lineages of blood cells and include anemia, leukopenia as well as thrombocytopenia, are among the most common complications of HIV infection (*1-3*). Among these hematologic disorders, anemia is the most common hematologic manifestation (*2,4,5*). In different studies, the prevalence of anemia in individuals with AIDS has been reported at 63% to 95%, making it more common than thrombocytopenia or leukopenia in AIDS patients (*6*). Hematological abnormalities, mainly anemia and leukopenia, in antiretroviral-naive HIV-infected patients result in poor antiretroviral treatment outcome and otherwise strongly predict mortality (*7,8*). Our previous study (*9*) showed that anemia is highly prevalent among adults with newly diagnosed HIV/AIDS in China. The overall prevalence of anemia among antiretroviral-naive HIV-infected patients was 51.9%. We found that older age, lower CD4 count and minority ethnicity are associated with an increased risk of anemia in antiretroviral-naive HIV-infected patients. However, so far the prevalence of leukopenia and thrombocytopenia in the Chinese population

**Address correspondence to:*
Dr. Hongzhou Lu, Department of Infectious Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China.
E-mail: luhongzhou@fudan.edu.cn

has not been well characterized. Considering such information for newly diagnosed HIV-infected patients may help to optimize antiretroviral treatment of HIV-infected individuals, we conducted a cross-sectional study to determine the prevalence of leukopenia and thrombocytopenia among Chinese adults with newly diagnosed HIV/AIDS, and to identify demographic and HIV-related factors associated with the presence of leukopenia and thrombocytopenia.

2. Methods

2.1. *Study population*

The cross-sectional survey was conducted among antiretroviral-naive HIV-infected patients from China's provinces and municipalities including Xinjiang, Jiangxi, Henan, Heilongjiang, Guangdong, Shaanxi, Guangxi, Hunan, Shanghai, and Yunnan during 2009 and 2010. The details of the study population have been described previously (*9*). In brief, antiretroviral-naive HIV-infected patients aged 18 years or more at the time of enrolment with confirmed HIV infection were eligible for this study. Patients who were on antiretroviral therapy (ART) were excluded.

2.2. *Blood samples*

Three-milliliter venous blood samples were collected from each patient. Full blood-count analyses were performed at the study laboratories in each province using a CELL DYN 3200 hematology analyser (Abbott Laboratories, USA). All the study laboratories successfully completed a standardization and certification program.

2.3. *Data collection*

Data were collected according to standardized criteria. All participants provided information on demographic characteristics, risk-behavior, and laboratory test results. Variables in the study included age, sex, HIV transmission route, and CD4 count. Age was denoted as < 40, 40-59, or ≥ 60 years. HIV transmission route was categorized as sexual contact (including homosexual or heterosexual), blood (including blood transfusion or injection drug use), or unknown transmission risk. CD4 count was denoted as < 50, 50-199, 200-349 or ≥ 350 cells/mm^3.

2.4. *Statistical analysis*

Statistical analysis was done using IBM SPSS Statistics version 19. Leukopenia was defined as total white blood cell (WBC) count $< 4 \times 10^9$/L while thrombocytopenia was defined as total platelet $< 100 \times 10^9$/L. Continuous variables were computed with standard methods and were expressed as mean and standard deviations (SD). Continuous variables were compared using *t* tests and analysis of variance. Categorical variables are reported as frequencies and percentage of each category. A chi-square test was applied for categorical attributes. The odds ratio and 95% confidence intervals were calculated to assess the relationship between each risk factor and the risk of leukopenia and thrombocytopenia; to adjust for the effects of potential confounders, we used multiple logistic regression models. All variables included in the models were determined a priori based on epidemiological importance and biological plausibility. Variables included in the models were age, sex, ethnicity, CD4 count, and HIV transmission route. The statistical test was two-tailed and performed at a level of statistical significance of 0.05.

2.5. *Ethics statement*

Written informed consent was obtained from all participants in accordance with this study's protocols and procedures approved by the Shanghai Public Health Clinical Center Ethics Committee. No patient identifiers were included in the dataset used for this analysis.

3. Results

3.1. *Demographic characteristics*

The study population is consisted of a total of 1,948 adults with newly diagnosed HIV/AIDS, of which the detailed information has been described in our previous survey (*9*). The study sample was primarily male (75.8%) (n = 1,476), the mean age was 40 years, 24.1% (n = 470) were ethnic minorities, and the mean CD4 count was 136 cells/mm^3. Most patients (74.2%) acquired HIV through sexual contact (n = 1,446).

3.2. *WBC counts among newly diagnosed HIV/AIDS patients*

The mean WBC count was $(5.37 \pm 3.04) \times 10^9$/L, which was higher among males than females (p = 0.001), and was also higher among ethnic minority patients than the Han patients (p = 0.001) (Table 1). The mean WBC count did not differ by CD4 count, age or HIV transmission route (p = 0.108, p = 0.239, p = 0.220).

3.3. *Platelet counts among newly diagnosed HIV/AIDS patients*

The mean platelet count was $(186.74 \pm 97.26) \times 10^9$/L, which was higher among ethnic minority patients than the Han patients ($p < 0.001$). The mean platelet count differed by CD4 count and HIV transmission route, the mean platelet count was highest among both patients with CD4 counts of < 50 cells/mm^3 (p = 0.002) and

Table 1. The WBC and platelet counts among newly diagnosed HIV/AIDS patients

Cohort	WBC (mean ± SD)	PLT (mean ± SD)
Number	1,948	1,948
Overall	5.37 ± 3.04	186.74 ± 97.26
Range	(0.53, 37.70)	(1, 626)
Sex		
Male	5.49 ± 3.02	186.05 ± 96.99
Female	4.98 ± 3.09	188.89 ± 98.19
p value for difference	0.001	0.581
Ethnicity		
Han	5.22 ± 2.85	181.99 ± 92.79
Minority ethnicity	5.83 ± 3.55	201.67 ± 108.90
p value for difference	0.001	< 0.001
CD4 count, cells/mm^3		
< 50	5.39 ± 3.59	196.42 ± 108.08
50-199	5.26 ± 2.95	178.54 ± 96.36
200-349	5.24 ± 2.18	178.87 ± 82.11
≥ 350	5.87 ± 1.95	188.00 ± 70.35
p value for difference	0.108	0.002
Age, years		
18-39	5.44 ± 3.26	187.57 ± 100.39
40-59	5.21 ± 2.61	184.92 ± 93.63
≥ 60	5.51 ± 3.23	189.21 ± 91.80
p value for difference	0.239	0.807
HIV transmission route		
Sexual contact	5.33 ± 3.00	192.06 ± 96.22
Blood	5.61 ± 3.28	168.75 ± 98.39
Unknown transmission risk	5.19 ± 2.91	177.01 ± 99.45
p value for difference	0.220	< 0.001

WBC: white blood cell; PLT: platelet; SD: standard deviation.

Table 2. Prevalence of leukopenia and thrombocytopenia among newly diagnosed HIV/AIDS patients

Cohort	Leukopenia	Thrombocytopenia
Number	1,948	1,948
Overall	33.2%	15.6%
Sex		
Male	31.2%	15.5%
Female	39.4%	15.7%
p value for difference	0.001	0.932
Ethnicity		
Han	34.1%	15.4%
Minority ethnicity	30.2%	16.0%
p value for difference	0.119	0.782
CD4 count, cells/mm^3		
< 50	41.5%	17.5%
50-199	33.4%	17.8%
200-349	26.5%	12.2%
≥ 350	8.2%	5.8%
p value for difference	< 0.001	< 0.001
Age, years		
18-39	32.3%	16.6%
40-59	34.6%	14.5%
≥ 60	32.9%	12.7%
p value for difference	0.585	0.284
HIV transmission route		
Sexual contact	33.0%	13.6%
Blood	32.1%	22.9%
Unknown transmission risk	37.0%	17.3%
p value for difference	0.521	< 0.001

patients infected with HIV through sexual contact ($p < 0.001$) (Table 1). The mean platelet count did not differ by sex or age ($p = 0.581$, $p = 0.807$).

3.4. *Prevalence of leukopenia among newly diagnosed HIV/AIDS patients*

Among the 1,948 patients, 646 (33.2%) had leukopenia (Table 2). The prevalence of leukopenia was higher among females than among males (39.4% versus 31.2%) ($p = 0.001$). The prevalence of leukopenia was 8.2%, 26.5%, 33.4%, and 41.5% among patients with CD4 counts of ≥ 350, 200-349, 50-199, and < 50 cells/mm^3, respectively. The prevalence of leukopenia increased with decreasing CD4 count ($p < 0.001$). The prevalence of leukopenia did not differ by ethnicity, age or HIV transmission route ($p = 0.119$, $p = 0.585$, $p = 0.521$).

3.5. *Prevalence of thrombocytopenia among newly diagnosed HIV/AIDS patients*

Among the 1,948 patients, 303 (15.6%) had thrombocytopenia (Table 2). The prevalence of thrombocytopenia was 5.8%, 12.2%, 17.8%, and 17.5% among patients with CD4 counts of ≥ 350, 200-349, 50-199, and < 50 cells/mm^3, respectively. The prevalence of thrombocytopenia showed an increasing trend with decreasing CD4 count ($p < 0.001$). The prevalence of thrombocytopenia was 13.6%, 22.9%, and 17.3% among patients infected with HIV through sexual contact, blood, and unknown transmission risk, respectively. The prevalence of thrombocytopenia differed by HIV transmission route, it was highest among patients infected with HIV through blood ($p < 0.001$). The prevalence of thrombocytopenia did not differ by sex, ethnicity or age ($p = 0.932$, $p = 0.782$, $p = 0.284$).

3.6. *Risk factors for leukopenia among newly diagnosed HIV/AIDS patients*

In a multivariate analysis using a logistic regression model, we analyzed factors associated with the presence of leukopenia. Female sex, Han ethnicity and lower CD4 count were significantly associated with an increased risk of leukopenia. HIV transmission route and age failed to show an association with the presence of leukopenia (Table 3).

3.7. *Risk factors for thrombocytopenia among newly diagnosed HIV/AIDS patients*

In a multivariate analysis using a logistic regression model, we analyzed factors associated with the presence of thrombocytopenia. Lower CD4 count and HIV transmission by blood were significantly associated with an increased risk of thrombocytopenia. Sex, ethnicity and age failed to show an association with the presence of thrombocytopenia (Table 3).

Table 3. Identification of risk factors for the presence of leukopenia or thrombocytopenia among newly diagnosed HIV/AIDS patients, results of the regression model

Cytopenia/Risk factor	*p* value	Odds ratio	95% CI
Leukopenia			
Female sex	0.001	1.471	(1.180, 1.835)
Minority ethnicity	0.010	0.738	(0.585, 0.930)
Age,per 20-year increment	0.570	1.045	(0.897, 1.218)
CD4 count, per increase of 150 cells/mm^3	< 0.001	0.610	0.547, 0.681)
HIV transmission route	0.418	-	-
Sexual contact	-	1.000	-
Blood	0.212	1.184	(0.908, 1.542)
Unknown transmission risk	0.555	1.111	(0.784, 1.573)
Thrombocytopenia			
Female sex	0.789	1.040	(0.778, 1.392)
Minority ethnicity	0.689	0.942	(0.703, 1.262)
Age,per 20-year increment	0.193	0.873	(0.711, 1.071)
CD4 count, per increase of 150 cells/mm^3	< 0.001	0.725	(0.630, 0.834)
HIV transmission route	< 0.001	-	-
Sexual contact	-	1.000	-
Blood	< 0.001	2.123	(1.571, 2.869)
Unknown transmission risk	0.210	1.322	(0.854, 2.045)

CI: Confidence interval.

4. Discussion

In present study, we observed a high prevalence of leukopenia and thrombocytopenia among newly diagnosed, antiretroviral-naive HIV-infected Chinese adults. Together with our previous study (*9*), the data indicate that hematologic abnormalities are relatively prevalent among antiretroviral-naive HIV-infected patients. The results from our studies further demonstrate that antiretroviral-naive HIV-infected patients exhibit a wide range of hematologic abnormalities. Anemia is the most common hematological abnormality, followed by leukopenia and thrombocytopenia. Cytopenias often cause symptoms and contribute to the complications suffered by AIDS patients like infections, anemia and bleeding. Medical professionals across all disciplines need to be aware of the hematological complications of HIV infection. Our findings constitute further evidence of the need for monitoring hematologic parameters of HIV-infected patients, both before ART initiation and routinely during treatment. Routine blood tests are currently recommended for HIV-infected patients both before and after initiating ART by HIV care and treatment guidelines.

In addition, our study showed that the overall prevalence of both leukopenia and thrombocytopenia increased with decreasing CD4 count, and that lower CD4 count was associated with an increased risk of both leukopenia and thrombocytopenia. Together with our previous investigation on anemia among the same population (*9*), these associations suggest that the stage of HIV-infection is an important determinant to pretreatment hematologic abnormalities. Hematologic manifestations of HIV infection are common and more frequent with progression of disease. A similar study demonstrated that blood cytopenias mainly occur in HIV patients with advanced immunosuppression and clinical stages (*10*). Another study found an association between CD4 count and hemoglobin level, neutrophil count, and platelet count (*7*). These results suggest that the presence of hematologic abnormalities in newly diagnosed HIV-infected patients is related to HIV infection itself. Therefore, it is important to identify patients with hematologic abnormalities and to consider HIV as a possible underlying cause.

The origin of hematological disorders in HIV infection remain to be studied. Current observations suggest that HIV infection may affect processes important during early stages of hematopoiesis or stem cell differentiation (*11*). Both a direct cytopathic effect of HIV on haemopoietic progenitors and an immune system mediated mechanism are involved in hematological abnormalities (*1*). Multiple interacting factors contribute to the hematological manifestations of HIV disease, it could be due to direct effects of HIV infection, opportunistic infections, lymphomas, malignancy or side effects of therapy. A study isolated the impact of HIV infection alone on hematologic manifestations and confirmed that these changes were reversible by ART (*12*). Therefore, control of the HIV infection will have the main role in the management of hematological manifestations of HIV.

Similar to our previous study on anemia in antiretroviral-naive HIV-infected patients, both demographic and HIV-related factors were associated with leukopenia and thrombocytopenia (*9*). In our study population, hematologic abnormalities were significantly associated with the factors of sex (only for leukopenia), age (only for anemia), ethnicity (except for thrombocytopenia), and HIV transmission route (only for thrombocytopenia). These findings provide focused targets for improving routine screening for hematologic

abnormalities in order to reduce the morbidity of the HIV-infected patients. Our findings have implications for the optimal choice of initial antiretroviral agents, monitoring of ART toxicities, and improvement of ART programs, especially in resource-limited countries.

Our findings are consistent with several published studies, which also indicate high leukopenia and thrombocytopenia prevalence and similar associated risk factors in HIV-infected patients. A study conducted among adult Zimbabweans showed that the prevalence of leukopenia and of thrombocytopenia was 11.7% and 24.7%, respectively (*13*). Leukopenia and thrombocytopenia were seen in 26.8% and 21.7% of HIV patients with CD4 counts less than 200 cells/mm^3 in India, respectively (*14*). Leukopenia and thrombocytopenia occurred in 24.3% and 8.3% of adult AIDS patients at initiation of ART in Uganda, respectively (*15*). The study in Uganda showed that the presence of any cytopenia was associated with female sex, decreasing CD4 count and decreasing body mass index. An investigation in South Korea found that the leading risk factor for cytopenia was AIDS status at initial presentation (*12*). Another study showed that neutropenia was associated with CD4 and platelet counts; and that thrombocytopenia was associated with country, gender, and chronic hepatitis B infection (*16*). However, studies in India (*17*) and Rwanda (*5*) did not find a significant correlation between thrombocytopenia and low CD4 count. The differences in the prevalence and risk factors could be attributed to demographic characteristics, geographical location, cut-off values used to define the cytopenias, and different stages of HIV illness in the study populations.

However, there are several limitations with our study. First, potential sample selection bias may have affected the findings. The HIV epidemic is serious in some provinces and among some most-at-risk populations in China. The study population is not representative of the entire HIV-positive population in China and so the results may not be generalizable. Second, this was an observational study, we were able to examine potential associations but were not able to assess causation, so it is not clear if the cytopenias preceded the HIV infection or *vice versa*. Third, cytopenias are associated with several factors including geographical location and comorbidities such as tuberculosis, hepatitis B infection, fever and oral candidiasis (*15*), these factors were not assessed in our study. Therefore, we were not able to determine the association between these factors and the prevalence of cytopenias. Furthermore, if these variables had been controlled for, some variables such as CD4 count might not have remained significant in the logistic regression model. In addition, we did not collect the information about concomitant medication use and were not able to assess its impact on cytopenias in this population.

In conclusion, leukopenia and thrombocytopenia are common among Chinese adults with newly diagnosed HIV/AIDS. Lower CD4 count is associated with an increased risk of both leukopenia and thrombocytopenia in antiretroviral-naive HIV-infected patients. We propose here that a routine assessment of these parameters is necessary for timely and adequate clinical management.

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